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CONSELHO EDITORIAL

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Centro Avançado de Neurologia e Neurocirurgia (CEANNE - suplemento 1)

Casos atípicos em doenças da base do crânio, teleneurologia e neurociências

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SUMÁRIO

BioSCIENCE Editorial
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Advanced Center for Neurology and Neurosurgery (CEANNE) Neurosciences in Transformation: From Anatomy to New Therapeutic Frontiers

Centro avançado de neurologia e neurocirurgia (CEANNE) Neurociências em transformação: da anatomia às novas fronteiras terapêuticas

Gustavo Rassier Isolan[1]

This Bioscience supplement brings together articles that reflect the vitality of research in neurology and neurosurgery. From the precision of microsurgical **approaches to the craniocervical junction and orbit to the challenges of basic research**, we see how anatomical tradition continues to guide increasingly safe and innovative practices.

In the field of neurological diseases, **conceptual and therapeutic advances in Alzheimer's disease stand out**, as well as **new therapies with anti-CD20 antibodies in multiple sclerosis**, symbols of the transition to an era of more personalized medicine. Completing the picture is the study of the **gut-brain axis in autism spectrum disorders**, which opens horizons for novel therapeutic strategies, and the analysis of the **cost-effectiveness of telemedicine in neurology**, a tool that brings specialists closer to previously underserved populations.

By integrating science, clinical practice, and innovation, this supplement reflects the efforts of medical professionals, researchers, and students from the CEANNE academic league.

Enjoy reading.

Gustavo Rassier Isolan

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BioSCIENCE Review Article
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Microsurgical anatomy: surgical approaches to the craniocervical junction

Anatomia microcirúrgica: abordagens cirúrgicas da junção craniocervical

Nicole Custódio Porto Silva, Isabela Fidalski Borba Coelho, Marcos Vinicius Sousa Varão,Kimberly Teixeira Barros, Júlia Michelini Pedrinelli Santos, Giovana Clausson Bitolo, Gustavo Rassier Isolan

ABSTRACT

Introduction: The craniocervical junction, located between the base of the skull and the first cervical vertebrae, is an anatomically and neurologically significant region. Due to its complexity, injuries and malformations in this area can lead to severe neurological complications, requiring precise surgical interventions. Advances in surgical techniques, such as endoscopic and microsurgical approaches, have expanded treatment options, enabling safer and less invasive procedures.

Objective: This study aims to review the most common surgical approaches to the craniocervical junction, including suboccipital, transoral, transnasal, far-lateral, and extreme-lateral techniques.

Method: A narrative review of the existing literature on craniocervical junction surgical techniques was conducted. The review included analyses of clinical cases, surgical outcomes, and technological advancements, such as the use of endoscopes and intraoperative neurophysiological monitoring. Comparative studies and case reports illustrating the advantages and limitations of each surgical approach were included.

Result: Detailed preoperative planning is essential for successful surgeries at the craniocervical junction. Radiological assessments using magnetic resonance imaging and computed tomography allow for precise three-dimensional analysis of the anatomical structures. Microsurgical techniques, including advanced microscopes and specialized instruments, have improved the safety of dissections and the preservation of critical structures like the vertebral arteries and cranial nerves. Intraoperative neurophysiological monitoring has proven effective in protecting neurological functions during surgery.

Conclusion: Surgery of the craniocervical junction requires an in-depth understanding of the local anatomy and neurovascular structures. The use of advanced microsurgical techniques and minimally invasive approaches, combined with detailed preoperative planning, is essential to optimize surgical outcomes and minimize complications. Technological innovations, such as intraoperative monitoring and endoscopic visualization, have contributed to safer and more effective procedures in this complex region.

KEYWORDS: Craniocervical junction surgery. Microsurgical techniques. Endoscopic approaches. Neurovascular considerations. Minimally invasive techniques

RESUMO

Introdução: A junção craniocervical, localizada entre a base do crânio e as primeiras vértebras cervicais, é uma região anatômica e neurologicamente significativa. Devido à sua complexidade, lesões e malformações nessa área podem levar a complicações neurológicas graves, necessitando de intervenções cirúrgicas precisas. Os avanços nas técnicas cirúrgicas, como as abordagens endoscópica e microcirúrgica, ampliaram as opções de tratamento, possibilitando procedimentos mais seguros e menos invasivos.

Objetivo: Este estudo tem como objetivo revisar as abordagens cirúrgicas mais comuns da junção craniocervical, incluindo as técnicas suboccipital, transoral, transnasal, lateral distante e lateral extrema.

Método: Foi realizada uma revisão narrativa da literatura existente sobre técnicas cirúrgicas da junção craniocervical. A revisão incluiu análises de casos clínicos, resultados cirúrgicos e avanços tecnológicos, como o uso de endoscópios e monitorização neurofisiológica intraoperatória. Foram incluídos estudos comparativos e relatos de casos ilustrando as vantagens e limitações de cada abordagem cirúrgica.

Resultado: O planejamento pré-operatório detalhado é essencial para cirurgias bem-sucedidas na junção craniocervical. As avaliações radiológicas por meio de ressonância magnética e tomografia computadorizada permitem a análise tridimensional precisa das estruturas anatômicas. As técnicas microcirúrgicas, incluindo microscópios avançados e instrumentos especializados, melhoraram a segurança das dissecções e a preservação de estruturas críticas, como as artérias vertebrais e os nervos cranianos. O monitoramento neurofisiológico intraoperatório tem se mostrado eficaz na proteção das funções neurológicas durante a cirurgia.

Conclusão: A cirurgia da junção craniocervical requer uma compreensão profunda da anatomia local e das estruturas neurovasculares. O uso de técnicas microcirúrgicas avançadas e abordagens minimamente invasivas, combinadas com um planejamento pré-operatório detalhado, é essencial para otimizar os resultados cirúrgicos e minimizar as complicações. Inovações tecnológicas, como monitorização intraoperatória e visualização endoscópica, têm contribuído para procedimentos mais seguros e eficazes nessa complexa região.

PALAVRAS-CHAVE: Cirurgia da junção craniocervical. Técnicas microcirúrgicas. Abordagens endoscópicas. Considerações neurovasculares. Técnicas minimamente invasivas.

Central Message

This article reviews the main surgical approaches for injuries to the craniocervical junction, highlighting the anatomical complexity of the region and the importance of advanced microsurgical techniques for safe and effective management. The focus is to provide a comprehensive guide for neurosurgeons, integrating anatomical knowledge and technological innovations to optimize surgical outcomes and minimize risks associated with different diseases affecting this critical region.

Perspective

Multidisciplinary article combining advanced knowledge in neuroanatomy, microsurgical techniques and neurovascular management. The analysis of the different surgical approaches emphasizes the need for detailed preoperative planning and the application of less invasive techniques whenever possible, aiming to preserve craniocervical stability and reduce neurological complications. The perspective is practical and surgeon-oriented, providing a critical view of the available options and their specific indications based on the location and type of lesion.

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INTRODUCTION

The craniocervical junction, located between the base of the skull and the first cervical vertebrae, is a complex region of great neurological significance. This anatomical area is responsible for the articulation between the skull and the spine, playing a crucial role in protecting the brainstem and upper spinal cord, as well as enabling vital movements of the head and neck. Due to its location and complexity, injuries and malformations in this region can lead to serious neurological complications, requiring precise and well-planned surgical interventions (Figures 1, 2, 3, 4 and 5).[1]

Advancements in surgical techniques, particularly the development of endoscopic and microsurgical approaches, have expanded treatment options for craniocervical junction lesions, allowing for safer and less invasive procedures. However, the choice of the ideal surgical approach depends on a detailed understanding of the local anatomy, the nature of the disease being treated, and the potential risks associated with each technique.[2]

This article reviews the main surgical approaches to the craniocervical junction, highlighting the indications and advantages of each, as well as the key considerations for preoperative planning and the application of advanced microsurgical techniques. By integrating anatomical knowledge with technological innovations, the aim is to provide a comprehensive guide for performing effective and safe surgeries in this challenging region.

METHOD

The methodology adopted in this article includes a narrative review of the existing literature on surgical techniques for the craniocervical junction, focusing on studies discussing suboccipital, transoral, transnasal, far-lateral, and extreme-lateral approaches. The review integrates analyses of clinical cases, surgical outcomes, and technological advances such as the use of endoscopes and intraoperative monitoring techniques. Comparative studies and case reports illustrating the advantages and limitations of each technique, as well as the importance of detailed and multidisciplinary surgical planning, were included. At the end, 21 articles were revised.

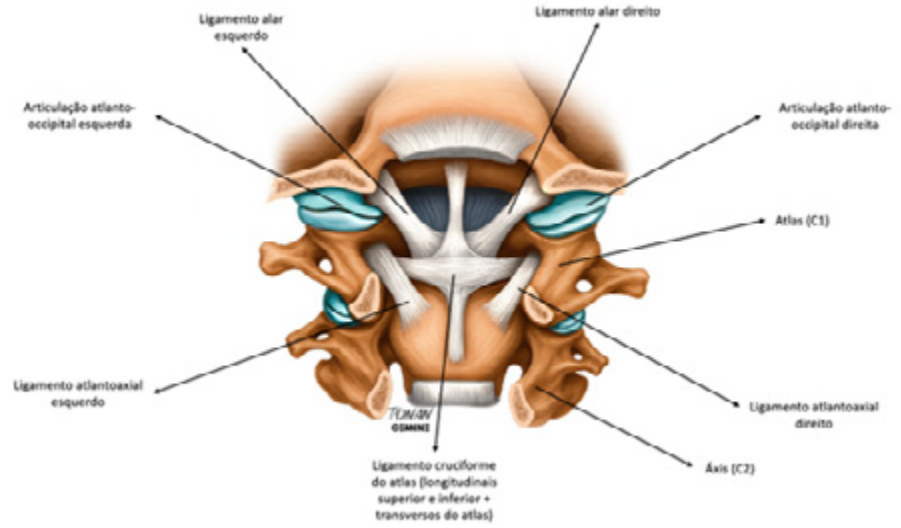

Figure 1 — Illustration of the ligaments of the craniocervical junction. Image copyrighted (Tonan/CEANNE)

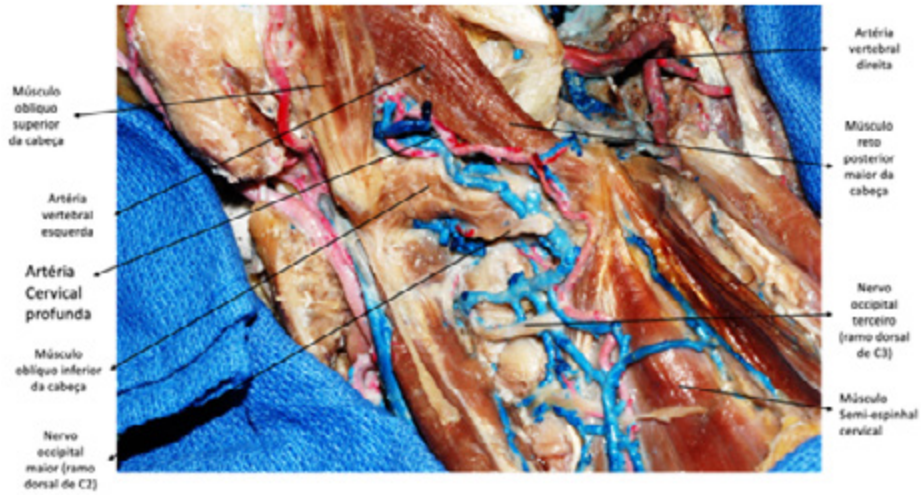

Figure 2— In the deeper layers of the posterior cervical region, there is a rich deep venous plenum (injected veins in blue), which is most abundant in the suboocpital triangle formed by the superior and inferior oblique muscles and the rectus capitis posterior major muscle.

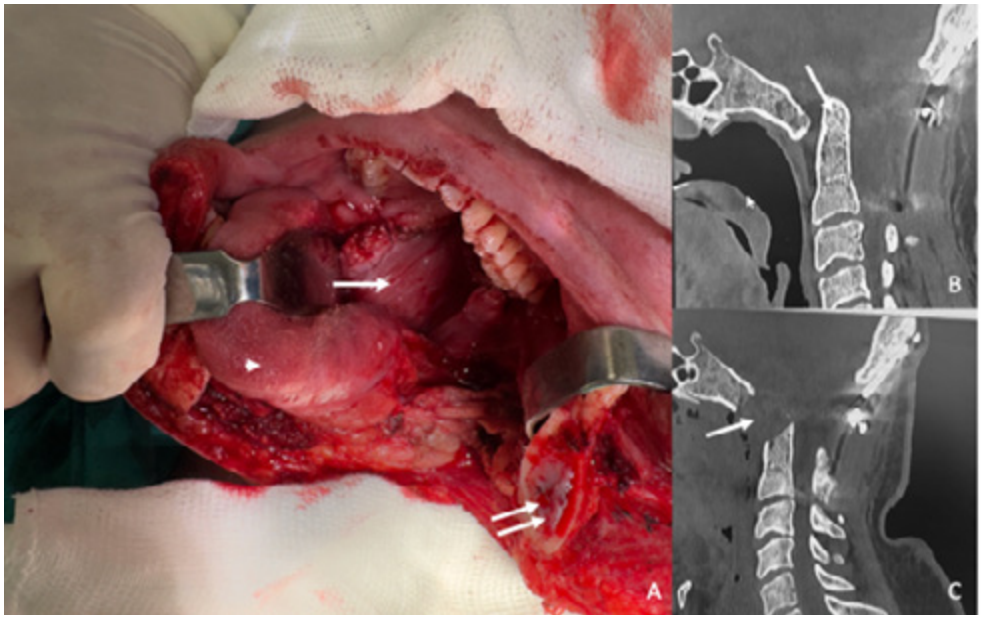

Figure 3 — A 32-year-old male patient with Chiari syndrome type 1 and invagination had previously undergone occipitocervical stabilization and posterior fossa decompression due to Chiari. Because significant motor deficits and respiratory failure persisted, an odontoidectomy and clivectomy of the inferior clivus were performed. Because the basilar impression was significant (angle difficulty with a purely endoscopic approach) and the patient's mouth opening was insufficient for a purely transoral approach, a transoral surgical approach with mandibulectomy was performed to adequately expose the surgical field, primarily due to the need for sufficient angulation for drilling the inferior clivus before resecting the invaginated odontoid process. The use of a neuronavigator was crucial in the surgical stages, and the patient recovered from the deficits and was weaned from the ventilator. A. Intraoperative image of the transoral approach with mandibulectomy (double arrow), providing a wide field of view of the posterior pharynx (arrow), after lateral displacement of the tongue (arrowhead). B. Preoperative sagittal CT scan showing invagination of the odontoid process (arrow). C. Postoperative CT scan showing removal of the odontoid process and inferior clivus (arrow).

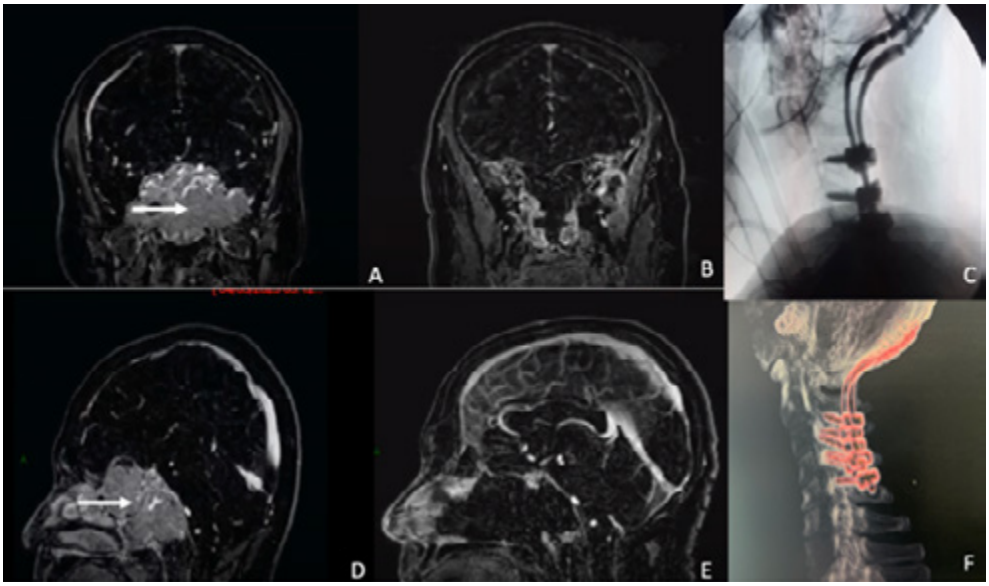

Figure 4 — Illustrative case of a male patient whose main complaint was that he experienced neck pain when looking downward and "had to hold his head to keep it from falling forward." Imaging studies revealed a large extradural tumor affecting the clivus, anterior fossa, pterygopalatine fossa, and infratemporal fossa bilaterally, as well as the petrous apex and cavernous sinuses bilaterally. In addition to new-onset neck pain, the patient reported dysphagia and hoarseness due to vocal cord paralysis diagnosed during laryngoscopy. Investigation of the craniovertebral junction (CVJ) revealed instability due to erosion of the occipital condyle. The patient underwent posterior occipitocervical fixation at the same surgical time. After the decubitus position was changed, an extended endoscopic endonasal approach was performed to remove the tumor component in the midline. The patient recovered all previous deficits one month after surgery. Although the endocrinological evaluation was normal preoperatively, serum prolactin levels were elevated postoperatively, indicating a "hook effect." The patient is undergoing treatment with cabergolide. A and B. Pre- and postoperative coronal T1-weighted MRI with gadolinium, respectively, demonstrating tumor resection of the midline component. C. Intraoperative X-ray after occipito-cervical fixation. D and E. Pre- and postoperative sagittal T1-weighted MRI with gadolinium, respectively, demonstrating tumor resection of the midline component (arrow). F. Postoperative CT scan with reconstruction demonstrating stability of the craniocervical junction due to occipito-cervical arthrodesis.

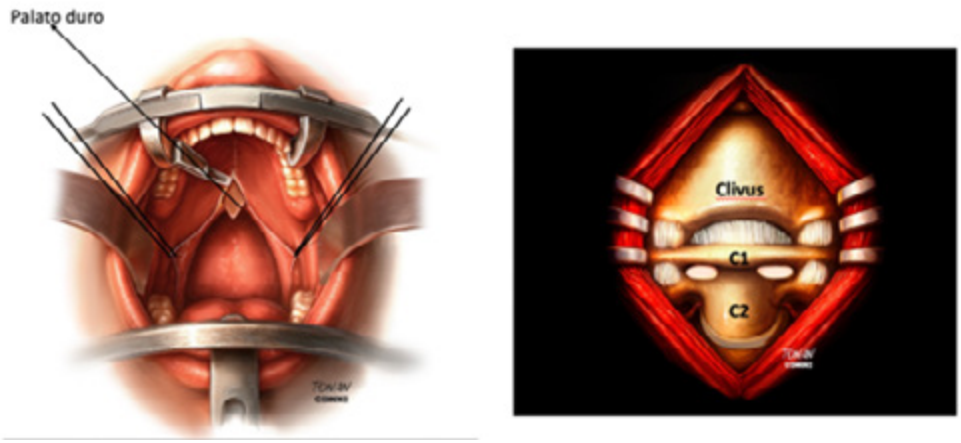

Figure 5 — The transoral approach is an option for expansive lesions of the craniocervical junction, preferably extradural, such as chordomas. A. Illustration of the transoral approach. B. Illustration of the structures commonly reached with this approach. Image copyrighted (Tonan/CEANNE)

DISCUSSION

The suboccipital approach is the preferred route for accessing the posterior portion of the craniocervical junction, allowing the treatment of lesions such as Chiari malformations, arachnoid cysts, and some neoplasms. This technique provides a wide view of the cerebellum, brainstem, and posterior fossa structures. According to Baird et al.[1] surgical exposure through the suboccipital approach offers a direct line for treating lesions located on the dorsal side, being highly effective for removing masses compressing the spinal cord and brainstem. The main advantage of this approach is the preservation of craniocervical stability, as the access is made through the opening of the occipital bone without the need to mobilize or remove the vertebrae.

The transoral and transnasal approaches are minimally invasive techniques primarily used to access anterior and central lesions of the craniocervical junction, such as ventral compressions caused by tumors or bone anomalies. Visocchi et al.[2] highlight that these routes are preferred because they avoid the need for large external incisions and provide a direct line to the skull base, reducing tissue manipulation. The transoral approach, for example, allows direct access to the anterior arch of the atlas and the body of the axis, while the transnasal may be chosen for higher lesions involving the skull base. The use of the endoscope in both techniques has increased the safety and efficacy of the procedures, allowing better visualization of anatomical structures during surgery.

The far-lateral and extreme-lateral approaches are indicated for lateral and anterolateral lesions of the craniocervical junction. These techniques allow access to areas not easily reached by more conventional routes, providing an oblique view of the foramen magnum and the craniocervical transition. Visocchi et al.[2] mention that these approaches are particularly useful for lesions involving the jugular foramen, lower cranial nerves, and vertebral arteries. The far-lateral approach, for example, offers the advantage of avoiding direct manipulation of the spinal cord while allowing access to anterior and lateral lesions such as meningiomas or metastatic lesions.

Preoperative planning

Detailed preoperative planning is essential for the success of surgeries at the craniocervical junction. Thorough radiological assessment is crucial for mapping the anatomical structures involved and identifying the characteristics of the lesion. The combined use of magnetic resonance imaging (MRI) and computed tomography (CT) allows for precise three-dimensional analysis, which is crucial for surgical planning. Baird et al.[1] and others3-5 emphasize that MRI is particularly useful for visualizing neural structures and intradural lesions, while CT is essential for assessing bone characteristics and planning the resection of structures such as the anterior arch of the atlas or the odontoid process.

Patient positioning is a critical aspect of preoperative planning, as it directly influences surgical exposure and intraoperative safety. Different positions, such as supine, prone, or semi-sitting, are chosen based on the selected surgical approach. According to Visocchi et al.[2,] the semi-sitting position, for example, is often used in suboccipital approaches because it allows gravity to retract brain structures, facilitating access to the posterior fossa. However, this position also presents risks, such as air embolism, which requires rigorous monitoring during surgery.[4,5]

Microsurgical techniques

The application of microsurgical techniques is essential for the precise manipulation of anatomical structures at the craniocervical junction. The use of advanced surgical microscopes enhances magnification and illumination of the operative field, allowing neurosurgeons to perform precise dissections safely. Guang-Lie L[4] highlights that the development of specific microsurgical instruments, such as fine forceps, delicate scissors, and high-precision suction devices, has revolutionized surgical techniques,

minimizing the risk of injury to nervous and vascular structures.

The preservation of critical structures, such as cranial nerves, vertebral arteries, and the spinal cord, is a priority during surgery at the craniocervical junction. Delicate and meticulous dissection techniques are employed to avoid damage to these vital structures. Guang-Lie L[4] describes the importance of following natural anatomical planes and using minimally invasive approaches to reduce surgical trauma. Additionally, the use of intraoperative neurophysiological monitoring, such as evoked potentials and electromyography, has proven effective in protecting neurological functions during surgery.[6]

Neurovascular considerations

The craniocervical junction is a complex anatomical region that integrates bone, ligamentous, neural, and vascular structures, requiring high precision in neurosurgical management. The craniovertebral junction is considered surgically challenging due to its anatomical characteristics. In this context, the neurovascular complexity of the anatomical region is an important consideration during surgical planning.[7]

The vertebral arteries, originating from the subclavian arteries, ascend along the cervical spine, curving around the C1 and C2 vertebrae before entering the skull, where they join to form the basilar artery. This basilar artery is fundamental for the blood supply to the posterior fossa and brainstem, playing a crucial role in the vascularization of these structures. The extracranial segment of the vertebral arteries (V3) is of surgical interest due to its proximity to the atlantoaxial joint, and detailed knowledge of this trajectory is essential to avoid injuries during surgical approaches. The intracranial segment (V4), in turn, renders the vertebral arteries vulnerable, requiring care during surgical manipulations to avoid damage to perforating branches supplying the brainstem.[8]

The craniovertebral junction also contains ligaments crucial for stability: the anterior longitudinal ligament, which becomes the anterior atlanto-occipital membrane, and the tectorial membrane, an extension of the posterior longitudinal ligament. The alar ligaments stabilize the junction by connecting the odontoid process to the occipital condyles and the atlas, while the transverse ligament keeps the odontoid against the anterior arch of the atlas.[8]

Exposing the vertebral arteries requires microsurgical techniques and careful dissection to minimize the risk of trauma and intraoperative hemorrhage. Controlling blood flow using temporary clips should be performed with extreme caution to prevent damage to the perforating branches. Temporary occlusion of these arteries can induce significant hemodynamic repercussions, especially in patients with compromised collateral circulation. In these cases, intraoperative Doppler ultrasound becomes a valuable tool for monitoring residual flow and assessing hemodynamic effects during surgery.[9]

Techniques to minimize the risk of intraoperative hemorrhages

In microsurgery of the craniocervical junction operative hemorrhages are critical priority. The adoption of a multidisciplinary approach, which includes detailed preoperative radiological planning and advanced intraoperative monitoring, is essential to minimize these risks and optimize surgical outcomes.[10]

Computed tomography is the method of choice for the initial evaluation of trauma, allowing detailed visualization of bone fractures and occipital-C1 subluxations or dislocations. However, it has limitations in assessing soft tissue injuries and the main stabilizing ligaments of the craniocervical junction. In these cases, cervical spine MRI stands out as an essential tool, allowing direct evaluation of the spinal cord and ligaments, which is crucial for managing complex injuries.[11]

During the surgical procedure, temporary vascular control, through the application of clips to the vertebral arteries or their main branches, may be necessary to reduce proximal and distal blood flow during dissection or lesion resection. However, the decision to apply temporary clips should be made with caution, taking into consideration the individual anatomy and the presence of sufficient collateral circulation. Intraoperative Doppler ultrasound has proven effective for monitoring flow and detecting possible complications, such as vessel stenosis or occlusions.[12-14]

The use of hemostatic agents such as fibrin glue, oxidized cellulose, and hemostatic sponges has been instrumental in controlling bleeding during microsurgery in the craniocervical junction region. However, care is needed when applying these agents close to vital structures, as accidental adhesions or excessive compression can result in iatrogenic injuries. The importance of achieving hemostasis during surgery cannot be overstated. Failure to effectively control bleeding may impair visualization of the surgical field and increase the risk of neurological complications. In addition to meticulous microsurgical techniques, advanced tools such as bipolar forceps, which allow safe coagulation close to nerve structures, are essential for successful management of vascular complications during surgery.[15-17]

The early identification and rapid management of vascular injuries are crucial to minimize the risk of severe neurological deficits. In situations where vascular injury occurs, immediate steps should be taken to control hemorrhage through the use of specific hemostatic instruments and techniques, such as bipolar coagulation and the application of hemostatic agents. When faced with complex vascular injuries, vascular reconstruction with sutures or grafting may be necessary. In these situations, the success of the procedure depends on the neurosurgeon's experience and surgical skill, as well as the availability of appropriate instruments and vascular materials.[18-21]

CONCLUSION

The surgical treatment of craniocervical junction diseases requires an in-depth understanding of the anatomy and the complex neurovascular structures involved. The use of advanced microsurgical techniques, associated with the adoption of minimally invasive approaches and precise preoperative planning, is essential to optimize surgical outcomes and minimize risks of complications. The integration of technological advances such as intraoperative neurophysiological monitoring and endoscopic visualization has contributed to safer and more effective surgeries, allowing for the precise management of lesions in this anatomically complex region.

Author´s contribution

Nicole Custódio Porto Silva: Conceptualization, Investigação
Isabela Fidalski Borba Coelho: Formal analysis, Methodology
Marcos Vinicius Sousa Varão: Validation, Writing – review & editing
Kimberly Teixeira Barros: Data curation, Writing – original draft
Júlia Michelini Pedrinelli Santos: Validation, Writing – review & editing
Giovana Clausson Bitolo: Formal analysis, Methodology
Gustavo Rassier Isolan: Project administration

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Microsurgical anatomy: surgical approaches to the orbit

Anatomia microcirúrgica: acessos cirúrgicos a órbita

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ABSTRACT

Introduction: The ocular orbit is a complex anatomical structure, and orbital surgical interventions require precision due to the proximity of vital structures such as nerves, blood vessels, and extraocular muscles. Advances in surgical approaches have improved the safety and effectiveness of treating orbital lesions.

Objective: This study reviews the main orbital surgical approaches, focusing on access techniques, preoperative planning, and microsurgical practices.

Method: A systematic literature review was conducted using PubMed, Scopus, and Web of Science, including case studies, reviews, and articles published between 1990 and 2024. The surgical approaches discussed include transconjunctival, transcutaneous, transcranial, and endoscopic techniques.

Result: Each approach offers specific advantages depending on the lesion location. Preoperative planning, using advanced imaging, and the application of microsurgical techniques are critical to the success of orbital surgeries.

Conclusion: Detailed knowledge of orbital anatomy and the application of advanced surgical techniques are essential for successful treatment of orbital lesions, ensuring better functional and aesthetic outcomes.

KEYWORDS: Orbital surgery. Orbital access techniques. Transconjunctival approach. Transcutaneous approach. Transcranial approach.

RESUMO

Introdução: A órbita ocular é uma estrutura anatômica complexa, e as intervenções cirúrgicas orbitárias requerem precisão devido à proximidade de estruturas vitais, como nervos, vasos sanguíneos e músculos extraoculares. Os avanços nas abordagens cirúrgicas melhoraram a segurança e a eficácia do tratamento de lesões orbitárias.

Objetivo: Este estudo revisa as principais abordagens cirúrgicas orbitárias, com foco nas técnicas de acesso, planejamento pré-operatório e práticas microcirúrgicas.

Método: Foi realizada uma revisão sistemática da literatura usando PubMed, Scopus e Web of Science, incluindo estudos de caso, revisões e artigos publicados entre 1990 e 2024. As abordagens cirúrgicas discutidas incluem técnicas transconjuntivais, transcutâneas, transcranianas e endoscópicas.

Resultado: Cada abordagem oferece vantagens específicas dependendo da localização da lesão. O planejamento pré-operatório, o uso de imagens avançadas e a aplicação de técnicas microcirúrgicas são fundamentais para o sucesso das cirurgias orbitárias.

Conclusão: O conhecimento detalhado da anatomia orbitária e a aplicação de técnicas cirúrgicas avançadas são essenciais para o sucesso do tratamento das lesões orbitárias, garantindo melhores resultados funcionais e estéticos.

PALAVRAS-CHAVE: Cirurgia orbitária. Técnicas de acesso orbital. Abordagem transconjuntival. Abordagem transcutânea. Abordagem transcraniana.

Central Message

Orbital surgery, given its complexity and proximity to vital structures, requires precise and well-planned surgical techniques. This article explores the main surgical approaches to the orbit, considering the importance of preoperative planning and microsurgical techniques to optimize clinical and aesthetic results. Understanding the different access techniques and the necessary care is essential to improve the effectiveness of interventions and minimize risks for patients.

Perspective

The ocular orbit, due to its intricate anatomy and proximity to vital structures such as nerves, blood vessels and oculomotor muscles, presents a significant surgical challenge. Advances in surgical techniques and the introduction of new approaches have enabled safer and more effective access to the orbit, improving the ability to treat lesions with precision. This article aims to provide a comprehensive overview of the different surgical techniques available, the necessary planning and microsurgical practices to maximize the success of orbital interventions.

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INTRODUCTION

The ocular orbit, a complex structure housing the eyeball and its appendages, presents a unique challenge for the surgeon due to its intricate anatomy and the proximity of vital structures such as nerves, blood vessels, and oculomotor muscles. Surgical interventions in the orbit require a highly precise and well-planned approach, as any error can result in significant functional or aesthetic impairment (Figure 2).[1-3]

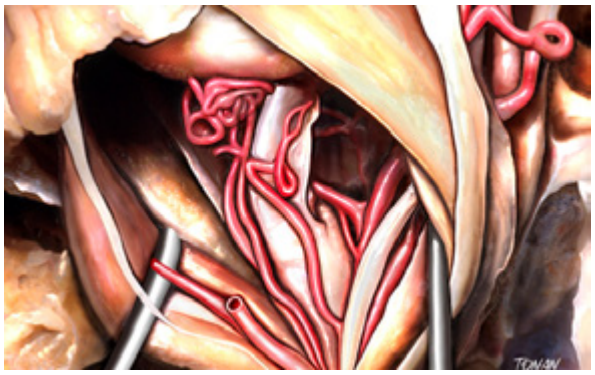

Figure 1 — Illustration of the microsurgical anatomy of the orbit. Copyrighted image (Tonan/CEANNE)

With advancements in surgical techniques and the development of new approaches, it is possible to access different parts of the orbit safely and effectively, minimizing risks to the patient. This article explores the main surgical approaches to the orbit, discussing the indications for each technique, the necessary preoperative planning, and the microsurgical practices that ensure the success of these interventions. By better understanding the available options and the necessary precautions, healthcare professionals can make more informed decisions when treating orbital injuries, providing better clinical and aesthetic outcomes.[4-6]

METHOD

Narrative review of the literature on surgical approaches to the ocular orbit was conducted, focusing on access techniques and microsurgical practices. The databases consulted included PubMed, Scopus, and Web of Science, using terms such as "orbital surgery," "orbital access techniques," and "orbital microsurgery." The review encompassed case studies, systematic reviews, and peer-reviewed articles published between 1990 and 2024. The analysis included the main surgical approaches - transconjunctival, transcutaneous, transcranial, and endoscopic - as well as the importance of preoperative planning and microsurgical techniques. The methodology also considered potential complications and management strategies associated with orbital interventions.

DISCUSSION

Surgical access

Orbital surgery involves a variety of complex approaches, each chosen based on the location and nature of the lesion, as well as the specific anatomy of the patient. The orbit is a highly sensitive anatomical region surrounded by vital structures such as nerves, blood vessels, and oculomotor muscles, requiring surgical precision and meticulous planning. This article explores the main surgical access techniques to the orbit, essential preoperative planning, and critical microsurgical techniques for the success of these interventions.[1]

The transconjunctival approach involves accessing the orbit through the conjunctiva, allowing exposure of the inferior and medial walls. This technique is particularly advantageous for lesions located in these regions, as it avoids skin incisions, thereby minimizing visible scars and aesthetic complications. Additionally, it allows direct access to target areas, facilitating the removal of lesions or repair of orbital fractures.[1]

The transcutaneous approach is performed through an incision in the skin, with subciliary and transcaruncular techniques being the most common. The subciliary incision is made just below the lower lash line, while the transcaruncular approach involves an incision in the lacrimal caruncle. Both techniques provide excellent exposure of the inferior and medial orbital walls. However, these approaches require careful attention to avoid aesthetic damage and ensure proper healing.[2]

The transcranial approach is used to access lesions located in the upper or deep portions of the orbit. This method involves removing part of the cranial vault, allowing direct access to the orbit and adjacent structures. This technique is often employed in cases of superior orbital tumors or situations where the lesion's extent requires a broad view and rigorous control over surrounding structures.[3]

The endoscopic approach utilizes endoscopes to access the orbit through the paranasal sinuses, offering a minimally invasive option for certain orbital lesions. With advancements in endoscopic techniques, this approach allows precise access with lower associated morbidity. It is particularly useful in cases of lesions involving the medial and inferior walls of the orbit, where direct access through the sinuses is possible.[4]

Preoperative planning

The success of any orbital procedure begins with detailed preoperative planning. Imaging assessment is crucial, involving advanced techniques such as magnetic resonance imaging and computed tomography to map the orbital anatomy and identify the lesion's exact location. In addition, three-dimensional planning can be employed to determine the best access path, thus minimizing the risk of damage to critical structures such as optic nerves and blood vessels. This planning phase is essential for choosing the most appropriate surgical approach and ensuring the procedure's success.[2]

Microsurgical techniques

Microsurgical techniques are indispensable in orbital surgery due to the proximity of vital anatomical structures. The use of surgical microscopes allows for magnified visualization of orbital structures, facilitating precise dissection and preservation of nerves and blood vessels. Fine and delicate instruments are used to minimize tissue trauma, and advanced suturing techniques are employed to ensure proper closure and reduce visible scarring.

Skill in performing these techniques is essential to avoid postoperative complications and achieve satisfactory aesthetic results.[4]

Neurovascular considerations

The orbit, as a confined space densely populated by nervous and vascular structures, presents considerable risks during surgical intervention. Understanding the surgical and topographic anatomy of the orbit is essential for preserving the functionality of these structures, regardless of whether the orbit is the primary focus of surgery or a passage to access deeper structures.[5]

The orbit can be divided into different compartments, such as the eyeball, the muscular cone, and the intraconal and extraconal spaces. These compartments house various neural and vascular structures, which are closely related. The muscular cone, which includes six extraocular muscles responsible for ocular movements, is one of the most critical regions. This cone converges at the orbital apex, forming the tendinous ring (or Zinn's ring), through which pass the optic nerve, oculomotor nerve, abducens nerve, the nasociliary branch of the ophthalmic nerve, and the ophthalmic artery. The separation of the muscular cone defines the intraconal and extraconal spaces, each with its own surgical considerations.[5]

Surgical indications

Treatment of orbital fractures and repair of traumatic injuries orbital fractures are frequent traumatic injuries following facial trauma, occurring in approximately 20% of severe facial injury cases and often accompanied by ocular damage.[6] These fractures can result from assaults, sports accidents, or other types of trauma, both direct and indirect, affecting the eyeball or the orbital, facial, and cranial bones.[7] The most common presentation of orbital fractures is associated with complex zygomatic fractures, which involve the cheekbone and, consequently, the lateral wall of the orbit.[8]

Potential complications and management

The orbital anatomy is a complex and critical region, highly susceptible to injuries that can result in visual and ocular motility complications. Surgical procedures involving the orbit, as discussed by Maroon and Kennerdell1 and Natori and Rhoton[3], present considerable risks of visual loss, diplopia, and restrictions in ocular movement. These complications may occur due to the proximity of delicate neural and vascular structures surrounding the orbit.

CONCLUSION

Orbital surgery requires detailed anatomical knowledge and a refined technical approach to ensure safe and effective outcomes. Each access technique -transconjunctival, transcutaneous, transcranial, and endoscopic - has its indications and advantages depending on the lesion's location and nature. Meticulous preoperative planning, utilizing advanced imaging technologies and mapping strategies, is crucial to minimize risks and optimize outcomes. Microsurgical techniques play a fundamental role in preserving vital structures and reducing postoperative complications. The continuous advancement in surgical techniques and complication management contributes to improving clinical and aesthetic outcomes in orbital surgeries.

Author´s contribution

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Wilson da Silva Rocha Vidal Neto: Formal analysis, Methodology
Maria Antônia Oliveira Machado Pereira: Conceptualization, Investigação
Giovana Clausson Bitolo: Data curation, Writing – original draft
Christopher Aquino Pereira Lima: Conceptualization, Investigação
Amanda Letícia Miotto: Formal analysis, Methodology
Gustavo Rassier Isolan: Project administration

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Multiple sclerosis and its treatment with anti-CD20+ therapy: a brief review

Usos e benefícios da terapia anti-CD20+ na esclerose múltipla: uma mini revisão

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ABSTRACT

Introduction: Multiple sclerosis is an autoimmune disease that affects the central nervous system. In this condition, the immune system attacks myelin, a substance that coats nerve fibers, causing damage to communication between the brain and the body. This can result in a wide range of symptoms, including muscle weakness, coordination difficulties, fatigue, visual disturbances, and even cognitive problems.

Objective: This article aims to gather recent advances in the treatment of multiple sclerosis with anti-CD20+ monoclonal antibodies, considering the emerging understanding of the involvement of B lymphocytes in the pathogenesis of the disease.

Method: Integrative review using PubMed and ScienceDirect as databases, utilizing the terms "Antigens CD20," "Multiple Sclerosis," and "Monoclonal Antibodies." Inclusion criteria for articles were a publication period of up to 5 years, English language, and freely available text.

Result: The discovery of the involvement of B lymphocytes in various stages of multiple sclerosis has enabled the use of pharmacological treatment with the use of anti-CD20+ monoclonal antibodies. This therapy has proven effective in treating early stages, reducing the rate of progression of debilitating symptoms in patients.

Conclusion: Due to their depletion of immune system cells, adverse effects such as type II hypersensitivity reactions and the emergence of opportunistic infections have been often observed.

KEYWORDS: Monoclonal antibody. Treatment. Immune cells.

Central Message

The efficacy and importance of the use of anti-CD20 monoclonal antibodies in the treatment of relapsing-remitting multiple sclerosis (MS), especially with the introduction of drugs such as ocrelizumab, has been highlighted. The text highlights the role of B cells in the pathophysiology of MS and the evolution of therapies targeting these cells, underlining the relevance of early treatment for better clinical and radiological outcomes.

Perspective

The use of anti-CD20 antibodies represents a significant advance in the management of MS, offering a more promising option in terms of controlling disease progression and reducing relapses. However, it also points to the need for careful monitoring due to the risk of adverse events and complications, emphasizing that therapy should be individualized and adjusted according to the stage of the disease.

RESUMO

Introdução: EM é doença autoimune que afeta o sistema nervoso central. Nessa condição, o sistema imunológico ataca a mielina, substância que reveste as fibras nervosas, causando danos à comunicação entre o cérebro e o corpo. Isso pode resultar em ampla gama de sintomas, incluindo fraqueza muscular, dificuldades de coordenação, fadiga, distúrbios visuais, e até mesmo problemas cognitivos.

Objetivo: Descrever os avanços no tratamento de EM com anticorpos monoclonais anti-CD20+.

Método: Revisão integrativa utilizando como banco de dados Pubmed e ScienceDirect, utilizando os termos "Antigens CD20", "Multiple Sclerosis" e "Antibodies Monoclonal". Os critérios de inclusão dos artigos foram período de publicação de até 5 anos, idioma em inglês e texto disponibilizado gratuitamente.

Resultado: Com a descoberta da participação de linfócitos B em diversos estágios de EM, possibilitou-se o uso de tratamento farmacológico com a utilização de anticorpos monoclonais anti-CD20+. Por agirem de forma a depletar célula do sistema imune, efeitos adversos se mostraram frequentes, como reações de hipersensibilidade tipo II e aparecimento de infecções oportunistas.

Conclusão: Esta terapêutica se mostrou eficiente no tratamento de estágios iniciais, com redução da velocidade de progressão de sintomas incapacitantes nos pacientes.

PALAVRAS-CHAVE: Anticorpo monoclonal. Células imune. Tratamento.

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INTRODUCTION

Multiple sclerosis (MS) is a neurological disease of an autoimmune nature that is manifested both through mild symptoms such as fatigue, tingling of the limbs, high sensitivity to touch and balance problems, as well as by more serious symptoms such as muscle spasms, chronic pain, cognitive problems, difficulty in daily activities such as speaking, eating and walking, and may even have cases of loss of vision and voice. The disease has a demyelinating and neurodegenerative character in the central nervous system, being the main cause of non-traumatic neurological disability in young adults.[1]

The pathological feature of MS is the formation of demyelinating lesions in the brain and spinal cord, which may be associated with neuroaxonal damage. The chronic inflammatory character of the central nervous system is caused by aberrant immune activation, resulting in damage to the myelin sheaths in the brain, spinal cord, and axonal loss.[2] Focal lesions are thought to be caused by infiltration of immune cells, including T cells, B cells, and myeloid cells, into the central nervous system parenchyma, with associated injury.[3]

The disease is predominant in women, aged between 18 and 55 years, and in Brazil its prevalence rate is close to 15 cases per 100,000 inhabitants.[4] The rate of hospitalizations increases from the age of 15 in both sexes and intensifies in the age groups of 20-29 years (22.2%), 30-39 years (28.6%), 40-49 years (21.8%), and 50-59 years (13.2%). Thus, 85.9% (24,986) of the total hospitalizations (29,088) occur between 20-59 years of age.[5]

Approximately 85% of newly diagnosed patients have the relapsing-remitting MS phenotype (RRMS or RRMS). After an average time of approximately 20 years, the vast majority evolve to the so-called "secondary progressive MS" phase (SPMS or SPMS).[6]

The treatment is diverse and has evolved over the years since its discovery. As it is a chronic disease, treatment is continuous and has the main objective of controlling acute attacks, controlling progressive worsening and remedying uncomfortable or disabling symptoms.[7] The pharmacological set used is diverse and consists of groups that focus on reducing symptoms. Immediately after diagnosis, 2 drug conducts follow: the first aims to reduce the time of the acute phase, and the second consists of trying to increase the interval between one outbreak and another.

For the first case, the reduction of the time of the acute phase, the management is done as in other autoimmune diseases: with the use of corticosteroids. In the second measure, which increases the interval between outbreaks, the use of immunosuppressants and immunomodulators help to expand the episodes of recurrence and the negative impact they cause in the lives of MS patients.

Although steroids do not affect the course of the disease, over time they have been shown to reduce symptoms, improve motor function, and shorten recovery time from acute attacks. Corticosteroids can be administered orally or parenterally, and it is assumed that their effect on the immune system depends on dose and duration.[8] Although long-term use of low-dose corticosteroids has been shown to be effective and relatively safe, shorter courses of high-dose corticosteroids are generally preferred to treat acute exacerbations of inflammatory disorders.[8]

However, the drug group responsible for the increase in the time of recurrence of clinical manifestations is more specific to the pathophysiology of the disease, especially in the action of the damage associated with inflammation caused by the perivenular infiltrate composed of T and B lymphocytes, macrophages, antibodies, and complement. DMT's (disease-modifying therapy) during the RRMS phase (Relapsing-remitting multiple sclerosis) has consistently demonstrated a significant impact on the annual relapse rate (ARR) and disability progression in the short term.[5-7]

From the immunological point of view, the existence of immune cell infiltrates in the central nervous system as a reason for the existence of the disease directs attention to its management and the search for new, more effective treatments. B lymphocytes are classified into regulatory and pro-inflammatory B cells, the latter with a role in regulating the polarization of T cells and, consequently, their inflammatory response. B cells are identified by markers expressed in all their stages of maturation, such as the CD20 transmembrane protein, which plays a role in cell differentiation and independent responses of T cells. The CD20 antigen is mostly associated with B cells; however, it is possible to find it in some T cell lines.[8]

In the inflammatory reaction, after the autoantigen is presented to the T lymphocytes, they induce the differentiation of B cells into plasmoblasts, which secrete antibodies, and can differentiate into plasma cells and maintain the emission of antibodies for long periods of time in the bloodstream. After differentiation into plasmoblasts, CD20 expression is reduced by downregulation but remains present in immunological memory B lymphocytes.[9]

In view of the importance of B cells in the pathophysiology of MS and, consequently, of the CD20 antigen, the various clinical trials aimed at the use of monoclonal antibodies specific to this protein are explained.[9] Monoclonal antibodies act to induce B cell depletion by means such as apoptosis, and may reach CD20-expressing T cells, which would contribute to greater efficacy in the treatment of MS, due to the involvement of both cells.[10]

Initially, MS was thought to be a T-cell-mediated demyelinating disease of the central nervous system. Disease-modifying therapies targeting T cells have, in fact, demonstrated remarkable efficacy in patients with relapsing-remitting MS (RRMS). However, these therapies also target B cells, and a CD20 B-cell-depleting monoclonal antibody, for example, ocrelizumab, which was recently approved for MS therapy and is effective not only in relapsing forms, but also in some patients with a primary progressive form.[10]

In view of the above, this study aimed to describe the advances reported in the literature on the treatment of MS with anti-CD20+ monoclonal antibodies.

METHOD

The present study is a narrative review of the literature, which used the DeCS/MeSH descriptors "Antigens CD20", "Multiple Sclerosis" and "Antibodies Monoclonal", intersected with the Boolean operator "AND", to search the PubMed and ScienceDirect databases. The selected period was from 2020 to 2023. Thus, 172 articles were found, according to the inclusion criteria (English language, period of publication, text available in full at the IP of the institution where the research was carried out and being inserted according to the guiding question of the research). A total of 98 review articles were excluded. In the end, 27 articles were analyzed, by title and abstract, of which 6 were selected to compose the present review, as they were in agreement with the guiding question and addressed the theme expressed by the review.

DISCUSSION

Although MS has traditionally been considered a T-cell-mediated autoimmune disease, in recent years, evidence about the participation of B cells in its pathophysiology has accumulated both in the early stage and with the progression of the disease. B cells have therefore emerged as an important target for several established MS therapies, including the use of interferon-β (IFN-β), fingolimod hydrochloride, and cladribine. However, more selective depletion of B cells can be obtained with the use of anti-CD20 monoclonal antibodies (mAbs), being a more promising and efficient therapy for the treatment of the disease.[11]

Of the antibodies approved until 2021, ocrelizumab, a humanized antibody applied intravenously, is considered the best and, therefore, the most indicated for use in patients with relapsed forms of the disease, showing excellent anti-inflammatory activity via inhibition of regulatory B cells and the ability to slow the progression of MS, which has been demonstrated in randomized phase III clinical trials.[12,13]

This antibody was approved in 2017 by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for patients with RRMS and PPMS. It can be used in a dose of 600 mg, administered fractionally into 2 doses of 300 mg, at an interval of 2 weeks between the first infusion and the second. After this period, a single dose of 600 mg every 24 weeks is indicated to maintain the therapeutic effects of the drug. In addition, ocrelizumab has shown promising results in individuals who have other autoimmune diseases, especially rheumatoid arthritis.[14]

Rituximab is a second-generation chimeric anti-CD20 (junction of human and mouse IGg1) that was approved in 1997 for B-cell lymphoma, but is being used off-label in several neurological diseases, including neuromyelitis optica (NMOSD), myasthenia gravis, and MS. There are several different rituximab dosing protocols; however, MS patients are most commonly being treated with 500 mg or 1000 mg intravenously every 6-12 months, in some cases after 2 initial injections 2 weeks apart.[15]

As for obinutuzumab, it has certain benefits in patients with membranous nephropathy associated with phospholipase A2 receptors. Ofatumumab, a fully humanized antibody, is applied subcutaneously and was initially developed for the treatment of chronic lymphatic leukemia.[16] It later received approval for the treatment of people with RRMS, a process in which it binds to a small extracellular loop of the CD20 membrane protein and acts by stimulating the c1q protein of the complement system, leading to cell lysis of regulatory B cells.[9,10]

Finally, ublituximab has also been approved for use in RRMS, as well as for the treatment of neuromyelitis optica spectrum disorder. It is a novel anti-CD20 monoclonal antibody that is glycoengineered to enhance the targeting of the response to B cells through cytotoxicity. Its development aims to allow the reduction of doses and the shortening of drug infusion times.[3,14]

The importance of an early start for anti-CD20+ therapies was also established. Treatment in the early stages, in all articles, was related to considerable improvement in both clinical and radiological outcomes of MS patients. This includes reduction in relapses (promoted by outbreaks of demyelination) as well as slower progression of the patient's disabling symptoms.

However, the presence of serious and varied adverse events, with some frequency, in patients who use these monoclonal antibodies, shows that the use of these drugs still requires adequate long-term monitoring and risk management. For ocrelizumab, in particular, the most common adverse effects were Infusion Related Reactions (IRR), possibly formed by type II hypersensitivity reactions. In addition, other problems arise from opportunistic infections of the upper respiratory tract (predominantly nasopharyngitis) and urinary tract. Serious infections also occurred in 1.3% of patients treated with ocrelizumab. Approximately 30% of patients also had hypogammaglobulinemia, which also significantly increases the risk of infection.[13-16]

CONCLUSION

The therapeutic approaches achieved throughout history, especially regarding MS, were of great scientific importance in the modern world. The pathophysiology, which for a long time was enigmatic, today has a better understanding and thus favored the evolution of more specific treatments. The use of the anti-CD20 monoclonal antibody in a disease with autoimmune and neurological characteristics evidences this achievement in the therapeutic evolution. The most recent articles have addressed the evolution of patients, and some cases not only in the RRMS phase, but also in PPMS. In addition, the use of anti-CD20 and its follow-up favor new perspectives of the pathophysiology of the disease, which still has some inconsistencies, after all, it is still a chronic disease. However, it is also important to point out that despite all the advances in anti-CD20 therapy, there are still some factors that must be evaluated, as it is a medication that is not exempt from causing complications and side effects. For these reasons, regular and long-term follow-up should be carried out. The application of medications in this pharmacological group should also be evaluated in the issue of the phase of the disease, as promising results may not be maintained depending on whether it is, for

example, the case of an SPMS, emphasizing in most cases early use.

Authors' contributions

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Explorando a inibição da bace: uma revisão sistemática dos potenciais tratamentos para a doença de Alzheimer

Exploring bace inhibition: a systematic review of potential Alzheimer's disease treatments

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ABSTRACT

Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of β-amyloid plaques and neurofibrillary tangles. BACE1 (β-site amyloid precursor protein cleaving enzyme 1) inhibition has been proposed as a therapeutic strategy to reduce β-amyloid production and slow disease progression. However, clinical trials on BACE1 inhibitors have yielded conflicting results regarding their efficacy and safety.

Objective: To evaluate the efficacy and safety of BACE1 inhibitors in Alzheimer's disease by synthesizing key clinical trial findings and biomarker outcomes.

Method: This systematic review followed the PRISMA 2020 guidelines. A literature search was conducted in PubMed and Cochrane Library databases using the terms "BACE inhibitor," "Alzheimer," "Beta-secretase," and "Amyloid beta." Only randomized controlled trials assessing BACE1 inhibitors in patients with mild-to-moderate Alzheimer's disease were included.

Result: Analysis of 15 selected studies revealed that BACE1 inhibitors significantly reduced β-amyloid levels in cerebrospinal fluid and plasma. However, they failed to slow cognitive decline, with some studies reporting functional worsening in treated patients. Adverse events included neuropsychiatric symptoms, sleep disturbances, brain volume reduction, and an increased incidence of severe side effects, leading to the discontinuation of several clinical trials.

Conclusion: While BACE1 inhibitors effectively lower amyloid biomarkers, the lack of cognitive benefits and associated risks raise concerns about their viability as a therapeutic strategy for Alzheimer's disease.

KEYWORDS: BACE inhibition. Systematic review. Treatment. Alzheimer's.

Central Message

BACE1 inhibitors have been shown to be effective in reducing brain amyloid load; however, they failed to demonstrate significant clinical benefits in slowing the progression of Alzheimer disease. In addition, adverse events, such as neuropsychiatric effects and unexpected brain structural changes, raise concerns about the safety of these therapies.

Perspectiv

Inhibition of BACE1 (β-site amyloid precursor protein cleaving enzyme 1) has emerged as a promising approach to modify the course of Alzheimer's disease, one of the most prevalent and debilitating neurodegenerative conditions. The therapeutic rationale is based on the interruption of the amyloid cascade, preventing the formation of βamyloid plaques, a central pathogenic element in the disease. However, despite advances in the development of BACE1 inhibitors, clinical trials have generated ambiguous results, raising doubts about the safety and efficacy of this strategy.

RESUMO

Introdução: A doença de Alzheimer (DA) é uma condição neurodegenerativa progressiva, caracterizada pelo acúmulo de placas de β-amiloide e emaranhados neurofibrilares. A inibição da enzima BACE1 (β-site amyloid precursor protein cleaving enzyme 1) tem sido proposta como uma estratégia terapêutica para reduzir a produção de β-amiloide e retardar a progressão da doença. No entanto, os ensaios clínicos com inibidores da BACE1 têm produzido resultados conflitantes quanto à sua eficácia e segurança.

Objetivo: Avaliar a eficácia e segurança dos inibidores da BACE1 na Doença de Alzheimer, sintetizando os principais achados clínicos e biomarcadores em ensaios clínicos randomizados.

Método: Esta revisão sistemática seguiu as diretrizes PRISMA 2020. A busca foi realizada nas bases de dados PubMed e Cochrane Library, utilizando descritores como "BACE inhibitor", "Alzheimer", "Beta-secretase" e "Amyloid beta". Foram incluídos ensaios clínicos randomizados que avaliaram a eficácia e segurança dos inibidores da BACE1 em pacientes com DA leve a moderada.

Resultado: A análise de 15 estudos selecionados revelou que os inibidores da BACE1 reduzem significativamente os níveis de β-amiloide no líquido cefalorraquidiano e plasma. No entanto, não demonstraram eficácia na desaceleração do declínio cognitivo, e alguns estudos relataram piora funcional nos pacientes tratados. Eventos adversos incluíram sintomas neuropsiquiátricos, distúrbios do sono, perda volumétrica cerebral e aumento da incidência de efeitos adversos graves, levando à interrupção de diversos ensaios clínicos.

Conclusão: Apesar da capacidade dos inibidores da BACE1 de reduzir biomarcadores amiloides, a ausência de benefícios cognitivos e os riscos associados à sua administração questionam sua viabilidade como estratégia terapêutica para a DA.

PALAVRAS-CHAVE: Inibição da BACE. Revisão sistemática. Tratamento. Alzheimer.

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting millions of people worldwide and posing a growing challenge to public health systems. Its prevalence is estimated to increase dramatically with the aging of the population, which amplifies its socioeconomic impact. In addition to the direct costs related to medical care, there is also a considerable burden on caregivers and patients' families. In view of this reality, it is essential to develop effective therapeutic strategies to slow or stop the progression of the disease.[1,2]

At the pathological level, AD is characterized by 2 main brain changes: the formation of beta-amyloid plaques and neurofibrillary tangles. The aggregation of the beta-amyloid peptide is considered an initial event in the degenerative process, being facilitated by the action of the enzyme BACE1 (Beta-secretase 1), which cleaves the amyloid precursor protein (APP). This process results in the production of fragments that are deposited in the brain, leading to synaptic dysfunction and neuronal death.[3,4] Thus, BACE1 inhibition emerges as a promising strategy to interrupt the amyloid cascade and potentially modify the course of the disease.[5-8]

Given the complexity and devastating impacts of AD, this review aims to explore the therapeutic potential of BACE1 inhibitors. Based on evidence from recent clinical trials, the benefits and limitations of this approach will be discussed, aiming to contribute to the understanding of the advances and challenges in the search for disease-modifying treatments.[9,10]

METHOD

This is a systematic literature review with a qualitative-quantitative approach, guided by PRISMA 2020. The guiding question of this review was elaborated following the PICO strategy, an acronym that consists of defining the population (P), the intervention (I), the comparison (C) and the outcome (O) of interest, resulting in the following question: Are BACE inhibitors effective for patients with Alzheimer's disease in terms of efficacy and safety in terms of response to treatment, remission of symptoms and adverse effects? Table 1 illustrates the strategy used.

TABLE – Application of the PICO strategy

P (population)	Patients with Alzheimer's disease
I (intervention)	Comparative treatment with BACE inhibitors vs. conventional treatments
C (comparison)	
O (outcome)	Efficacy and safety (response to treatment, remission of symptoms and adverse effects)

To answer this question, a systematic search was carried out in the electronic databases Medline/PubMed, and Cochrane Library. The variables of methodological elucidation to compose the theoretical framework were the following descriptors, based on the Health Sciences Descriptors (DeCS/MeSH) platform, combined with the Boolean operator "AND": " BACE inhibitor"; "Alzheimer 's"; "Beta secretase"; "Amyloid beta"; "Therapeutic targets", resulting in the following search strategy: "Bace inhibitor and Alzheimer"; " Beta secretase and Alzheimer's"; "Amyloid beta and BACE inhibitor"; "Therapeutic targets Beta-secretase". In addition, the bibliographic references of the selected articles were consulted to identify possible relevant studies not retrieved in the initial search. The studies eligible for inclusion in this review were those that met the following criteria: randomized controlled trials that evaluated cognitive training after intervention by BACE inhibitors, reporting at least one of the outcomes of interest. Studies with laboratory specimens, studies that included treatment without involving BACE inhibitors, preclinical studies, review articles, and letters to the editor were also excluded.

Studies published in Portuguese, English or Spanish were included. Studies that did not have any of the outcomes of interest or were published in other languages were excluded, as well as studies with laboratory specimens, studies on Alzheimer's treatment without BACE inhibitors, review articles, and letters to the editor.

To evaluate the effectiveness of the research technique and eliminate duplicate work, the Rayyan software from the Qatar Computing Research Institute (QCRI) was used. Two independent reviewers conducted the selection of studies, the extraction of data from Excel spreadsheets, and the evaluation of the methodological quality of the included studies, following the criteria of PRISMA 2020. The extracted data include study characteristics (authors, year, country, study type, sample size, patient age, duration of follow-up) and outcomes (response rates, remission, defined criteria, and major adverse events). Figure describes the research process, as well as the results of the search performed.

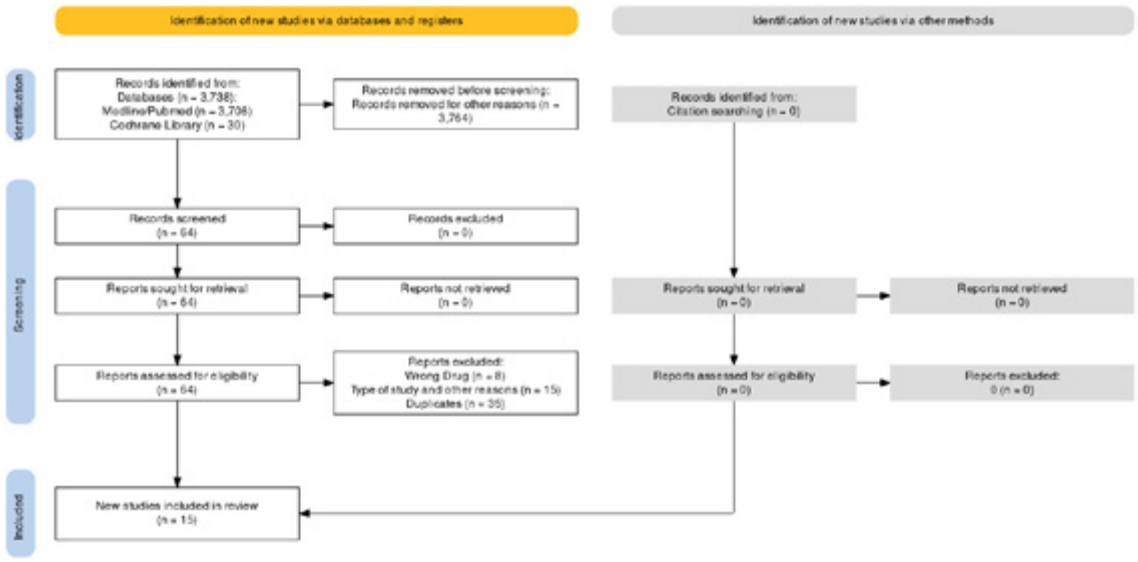
DISCUSSION

During the systematic search based on the research strategies, 3738 references from the Pubmed and Cochrane Library electronic databases were identified, and 3674 texts were excluded because they did not have the stipulated design or because they did not meet the objective of the present study. Sixty-four articles were accessed to verify eligibility, among which, after screening with the Mendeley software, 35 duplicates were removed, 8 were excluded because they were not BACE inhibitors, and another 15 because they did not agree with the methodology.

Thus, a total of 15 articles were selected for the present review.

In a randomized, double-blind, placebo-controlled study conducted in Japan and Europe, individuals with abnormal CSF Aβ 1–42 levels were selected and diagnosed as clinically asymptomatic (preclinical AD) who were cognitively and functionally normal (Clinical Dementia Score [CDR] of 0), or diagnosed with MCI due to AD who had some limited cognitive impairment, but they were

FIGURE — Application of the PRISMA flowchart



still functionally normal and therefore did not have dementia. In addition, neoplastic patients and those with other comorbidities were excluded, and tests were performed to adequately ascertain the cognitive capacity and metabolic levels of these patients. Patients received atabecestat 50 mg, followed by comparison of baseline CSF levels of the following biomarkers: Aβ 1–40, Aβ 1–42, APP fragments, p-tau 181p, and t-tau, in which it was observed that mean plasma concentrations of atabecestat increased with increasing dose, and no major differences in concentration-time profiles were observed between the atabecestat 10 and 50 mg groups on days 1 and 28 for Caucasian and Japanese participants, and between the preclinical AD and MCI groups due to AD and that individual CSF concentrations at day 28 also increased with increasing free plasma concentrations of atabecestat. Thus, model simulations confirmed that 10 mg and 50 mg atabecestat once daily can achieve reductions of 60–70% and 90% of Aβ 1–40, respectively, and overall, atabecestat was well tolerated, the incidence of TEAE in both studies was not significantly different from that of placebo, and no new safety signals were identified. In addition, the incidence of treatment-emergent adverse events (TEAEs) was low; however, the atabecestat 50 mg group experienced nausea (n = 1), Alzheimer's-type dementia (n = 1), headache (n = 1), and possibly related to the study drug was urticaria (n = 1). Finally, despite the results found, this study is limited because it is short-term and in a limited number of patients with early-stage AD.[11]

According to Fleischer et al.[6,] in its multicenter randomized controlled study with placebo and LY450139, individuals who received stable doses of cholinesterase inhibitor drugs or memantine were included, in which adverse effects such as skin and subcutaneous tissue problems with a p value = 0.05, color changes, and transient intestinal obstruction were included. However, plasma Aβ 40 concentration was reduced by 58.2% for the 100 mg group and 64.6% for the 140 mg group with p <0.001, but without any significant reduction in Aβ values in cerebrospinal fluid, as well as variations in cognitive or functional measures. Thus, although the study presented a small scale, it was possible to find that LY450139 was generally well tolerated at doses of up to 140 mg/d for 14 weeks, despite requiring clinical follow-up. In addition, decreases in plasma Aβ concentrations were consistent with inhibition of γ-secretase.

In the randomized study by Streffer et al.[12] a screening based on the following parameters: general health status, level of cognition, magnetic resonance imaging and cerebrospinal fluid biomarkers, having early and age-related Alzheimer's disease, as well as being aged between 50 and 90 years. Thus, after the study was applied to the target population, a positive association was found for the treatment of AD patients with JNJ-54861911, a potent inhibitor of BACE, resulting in strong reductions in plasma (10 mg: 83%; 50 mg: 93%) and CSF (10 mg: 67%; 50 mg: 90%) for having a central nervous action. In addition, sAPPη peptides decreased while sAPPα increased up to 2-fold and no change was observed in total sAPP, either in healthy elderly patients, and individuals with early AD.

In addition, 2 randomized phase I clinical trials, analyzed by Alexander et al.[1,] demonstrate that AZD3293 was well tolerated at all doses tested, with no serious adverse effects occurring. At first, a significant reduction in the levels of Aβ peptides in plasma and cerebrospinal fluid was observed, with prolonged suppression, even with a weekly dose regimen. Subsequently, the doses of 15 mg and 50 mg resulted in reductions of ≥64% and ≥78%, respectively, suggesting an effective effect on the reduction of amyloid load, a crucial target in the treatment of AD. Additionally, the data indicate a potential disease-modifying effect, reflecting in

improvements in patients' cognition and function. However, the small sample size and the absence of formal statistical tests limit the generalization of the results, highlighting the need for additional studies for validation.

In the meantime, a multicenter, randomized, double-blind, placebo-controlled study evaluated 209 outpatients, aged 50 to 90 years with a diagnosis of mild to moderate AD, treated with fixed doses of avagacestat, administered over 24 weeks. The results showed that the 25 mg (77.5%) and 50 mg (74.1%) doses were well tolerated, while the 100 mg and 125 mg doses resulted in higher discontinuation rates, with 48.1% and 64.7% of patients discontinuing treatment due to adverse events, predominantly gastrointestinal and dermatological, both of a dose-dependent nature ($p < 0.05$). In addition, analyses of cerebrospinal fluid biomarkers revealed significant reductions in Aβ42 isoforms ($p = 0.04$), suggesting effective engagement of the therapeutic target. There were also numerical declines in T-tau and P-tau, although these did not reach statistical significance ($p > 0.05$).

However, higher doses were associated with trends of cognitive worsening, with a mean decrease in ADAS-Cog score of 1.2 points, although no clear evidence of neurodegeneration such as brain atrophy or CSF tau elevation was observed. These findings indicate that lower doses of avagacestat are safe and promising for future investigations, provided there is close follow-up of adverse events and cognitive responses.[13]

Similarly, Egan et al. 5, used verubecestat at doses of 12 mg, 40 mg, or placebo in a 78-week trial evaluating 1,958 participants aged 55 to 85 years. During the period, 39 (6.0%) of patients in the 12 mg group, 49 (7.5%) in the 40 mg group, and 31 (4.7%) in the placebo group withdrew due to adverse events. What's more, the results showed that there was no significant difference in cognition and function between the treated groups and the placebo, with cognitive decline observed in all groups. However, there was a significant reduction in amyloid burden in the verubecestat groups, but this did not translate into clinical benefits.

In the following study, Egan et al.[5,] randomized 1,454 patients with criteria similar to the above, and verubecestat also did not show superior efficacy compared to placebo. Furthermore, the treated groups had higher rates of progression to dementia, with the 40 mg group showing significantly lower performance. In addition, hippocampal volume decreased from 6.1% in the placebo group to 6.[5-]6.7% in the verubecestat groups and the concentration of Aβ in the cerebrospinal fluid decreased by more than 60% in both treated groups, indicating drug action.

In 2 other studies by Egan et al.[3-5] more frequent adverse events were reported among the treated groups, including rashes and other symptoms, with a total of 9 deaths occurring in the 12 mg group, 12 in the 40 mg group, and 5 in the placebo group. The safety analysis highlighted an increase in suicidal ideation and nervous system-related events in the treated groups. However, despite reductions in biomarkers, the data suggest that AD progression may not be dependent on Aβ production, raising questions about the amyloid hypothesis of the disease.

In the verubecestat study, 118 patients (placebo: n = 37, 12 mg: n = 31, 40 mg: n = 50) were analyzed, measuring biomarkers in cerebrospinal fluid over 78 weeks, with mean NF-L concentrations (pg/mL) ranging from 1509 (baseline) to 1875 (placebo) and 1723 (baseline) to 1937 (40 mg verubecestat). The mean UCH-L1 scores were 2206 (placebo) for 2556 and 2768 (12 mg) for 2900. In addition, for total tau, the averages were 265 (placebo) for 284 and 319 (40 mg) for 311, while GFAP ranged from 32,071 (placebo) to 33,894 and 37,401 (40 mg) to 42,850, despite there being no significant differences from placebo for NF-L or other biomarkers.[7] In the LY3202626 study, which included 316 patients with mild Alzheimer's dementia, only 47 completed, leading to discontinuation due to the low likelihood of slowing cognitive decline. There were also no significant changes at 52 weeks between the groups, and psychiatric adverse events increased, although there were no deaths or related serious events, and the treatment did not significantly impact the brain tau load measured by flortaucipir.[14]

According to Lopez et al.[9,] the Generation program evaluated CAD106 and umibecestat, focusing on APOE4 patients at high risk of developing AD. Participants were monitored for 60 to 96 months, and the results indicated that APOE4 carriers may be less responsive to treatment due to rapid amyloid deposition. In addition, the study highlighted limitations in generalizing the results to people without the APOE4 allele, suggesting that the treatment may be less effective if not given early. However, Lynch et al.[10] looked at 70 subjects randomized to placebo or elenbecestat, with 61% completing the study. The group receiving 50 mg/day of elenbecestat demonstrated statistically significant reductions in PET SUVR in subgroups: -5.8% ($p = 0.013$) for florbetaben and -13.6% ($p = 0.014$) for florbetapir. In terms of cognitive decline, the 50 mg/day group showed 30% less decline in CDR-SB, although without statistical significance ($p = 0.55$). A subgroup with baseline PET SUVR between 1.4 and 1.9 showed 72% less decline in CDR-SB compared to placebo.

In this context, BACE inhibitors, such as LY2886721 and verubecestat, show important pharmacodynamic effects, but also present significant challenges. LY2886721 demonstrated a substantial reduction in amyloid-β (Aβ) levels in plasma and CSF, as well as promising results in animal models, with a reduction in Aβ in the hippocampus and cortex. However, safety concerns have emerged, such as abnormal elevations of liver enzymes in patients, resulting in the interruption of phase 2 clinical trials.[15] On the other hand, verubecestat, despite also impacting Aβ, was associated with a brain volumetric loss detected as early as week 13, with no further progression until

week 78. This volumetric effect was not directly correlated to amyloid load, raising hypotheses that the changes could be linked to the amyloid plaque microenvironment, inflammation, or fluid reorganization.[15]

Finally, Wessels et al.[13] in their studies with APECS and AMARANTH investigated the cognitive effects of BACE inhibitors verubecestat and lanabecestat in participants with early AD and mild cognitive impairment (MCI). In APECS, 1,454 participants were randomized, 485 to verubecestat 12 mg, 484 to verubecestat 40 mg, and 485 to placebo, while in AMARANTH, 2,218 participants were randomized between lanabecestat and placebo. The results demonstrated that verubecestat resulted in cognitive worsening, particularly in episodic memory and attention, from week 13 onwards, with a greater effect for the 40 mg dose, although the dominance of executive function showed improvements. In AMARANTH, lanabecestat showed significant worsening in measures such as RBANS score and digit symbol coding, with more pronounced effects for the 50 mg dose. However, in both studies, improvements in letter fluency were maintained over time, although category fluency stabilized after week 78.

The studies analyzed different drugs in order to understand the efficacy of drugs in the treatment of AD and their safety, since such drugs have adverse effects, most of them severe, which make adherence unfeasible, among them gastrointestinal and dermatological ones.

In the article by Alexander et al.[1,] titled "AZD3293 a novel BACE1 inhibitor: pharmacokinetics and effects on plasma and CSF a-beta peptides following multiple-dose administration in Alzheimer's disease patients," the authors investigate the effects of lanabecestat, a BACE1 inhibitor, on the reduction of beta-amyloid peptides, which are crucial in the pathogenesis of AD. Regarding the efficacy with the drug, there was a significant reduction in the levels of Aβ peptides in both plasma and cerebrospinal fluid, in which multiple doses of lanabecestat resulted in a reduction of up to 78% in plasma levels of Aβ peptides at doses of 50 mg or more, and a reduction of up to 76% in cerebrospinal fluid. In addition, single doses of 5 mg or more were sufficient to reduce plasma concentrations of Aβ 40 and Aβ 42 by more than 70%, with effects prolonged for up to 3 weeks, and for safety it was well tolerated and without serious adverse effects.

In the article by Coric et al.[2] They evaluated the safety and tolerability of avagacestat, a gamma-secretase inhibitor, in patients with mild to moderate AD. The results indicated that doses of 25 to 50 mg of avagacestat were well tolerated by the study participant but showed no significant efficacy in reducing the levels of beta-amyloid in the cerebrospinal fluid. In contrast, higher doses, from 100 to 125 mg, resulted in a significant reduction in beta-amyloid protein in the cerebrospinal fluid. However, these doses have been associated with considerable adverse effects, including gastrointestinal and dermatological problems such as maculopapular rashes, pruritus, and increased incidence of non-melanoma skin cancer.

In addition, higher doses of avagacestat worsened participants' cognition, without the authors being able to clearly identify the reason for this adverse effect.

The studies conducted by Egan et al.[3-5] and Kennedy et al.[7] in the EPOCH clinical trial investigated the use of the BACE-1 inhibitor, verubecestat (MK-8931), in patients with mild to moderate Alzheimer's. Verubecestat was evaluated at doses of 12 mg and 40 mg, focusing on adverse effects, biomarkers, and brain volumetric changes. The results indicated that verubecestat reduced cerebrospinal fluid Aβ concentrations and brain amyloid load, but failed to reduce cognitive or functional decline compared to placebo. The second paper revealed on MRI greater brain volume atrophy in the verubecestat-treated group, especially in amyloid-rich regions, from 13 to week 78. This volumetric loss was not associated with progressive neurodegeneration, suggesting changes in the microenvironment of amyloid plaques, possibly due to inflammation or changes in fluid organization.

The drug was well tolerated, but adverse effects associated with verubecestat included increased falls, injuries, syncope-like events, sleep disturbances, psychotic symptoms, anxiety, weight loss, and dermatological events similar to those seen in the study conducted on avagacestat. There was also a higher incidence of suicidal ideation, with 2 completed suicides and 1 attempt.

It is noteworthy that both avagecast and verubecestat showed a reduction in amyloid AB concentration, but without improvement in cognitive aspect. The authors question whether the pathophysiology of the disease, therefore, would be correct.

CONCLUSION

From the studies analyzed, it can be concluded that BACE inhibitors are able to reduce the concentrations of β-amyloid protein in plasma and cerebrospinal fluid. In addition, these drugs do not produce serious adverse events in relation to the use of placebo, with gastrointestinal and dermatological events being predominant, which are not tolerated at high doses. However, in regard to the prognosis of AD patients, few studies have obtained clinical improvement recorded in studies, with a predominance of those with a limited number of patients analyzed. Other studies did not analyze the parameter in question or did not obtain a correlation between a reduction in beta-amyloid protein and an increase in the cognitive potential of the participants, with an increase in the progression of cognitive decline being recorded. Thus, although BACE have the potential to decrease plasma and cerebrospinal fluid concentrations of substances involved in AD, the disease-modifying effect is still uncertain.

Authors' contributions:
Wilson da Silva Rocha Vidal Neto: Formal analysis, Methodology
Guilherme Nobre Nogueira: Validation, Writing – review & editing
Rafaela Fernandes Gonçalves: Project administration
Maroan Soraia Santos Navas Ribeiro: Project administration
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Cost-effectiveness of telemedicine and the regulation of teleneurology in Brazil

Custo efetividade da telemedicina e a regulação de teleneurologia no Brasil

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ABSTRACT

Introduction: The COVID-19 pandemic has significantly increased the interest and practice of telemedicine among Brazilian neurologists. Before the pandemic, only 18.5% used it, but this number rose to 56.2% after its onset. Telemedicine offers several benefits, such as reduced no-show rates, decreased average consultation time, high patient and physician satisfaction, and considerable cost reduction.

Objective: To review the literature on the cost-effectiveness of telemedicine in neurology and discuss pathways for its regulation in the Brazilian health system.

Method: This systematic review followed a rigorous methodological process. Databases such as PubMed, Medline (BVS), and Science Direct were used. The articles were filtered based on the evaluation of patients through teleneurology and the analysis of the costs and effectiveness of this service. Only original studies and clinical trials in English or Spanish were included, while duplicate and review articles were excluded.

Result: A total of 29 articles focused on the topic were included in this review.

Conclusion: Telemedicine in neurology is cost-effective and offers several advantages, such as cost reduction, improved patient quality of life, and increased access to specialists, and holds promise for improving care in rural and remote areas. However, adequate regulation, standardization of clinical and technical protocols, and financial sustainability of programs are essential for its successful implementation. Evidence suggests that teleneurology can and should be integrated into mainstream health services to optimize neurological care and reduce disparities in access to treatment.

KEYWORDS: Cost-effectiveness. Telemedicine. Teleneurology.

Central Message

The cost-effectiveness analysis of telemedicine is crucial to assess its economic and clinical impact, especially in the context of teleneurology. This modality uses digital technologies to offer neurological diagnoses and treatments at a distance, and it is essential to consider how regulation in Brazil influences its implementation.

Perspective

The regulation of teleneurology in Brazil is a key point to ensure its efficiency and safety. Studies show that adequate regulation can promote the reduction of health costs, improve access to specialists, and optimize the management of neurological diseases, proving to be essential to maximize the benefits of telemedicine in the country.

RESUMO

Introdução: A pandemia de COVID-19 aumentou significativamente o interesse e a prática da telemedicina entre os neurologistas brasileiros. Antes da pandemia, apenas 18,5% a utilizavam, mas esse número subiu para 56,2% após seu início. A telemedicina oferece vários benefícios, como redução da taxa de não comparecimento, diminuição do tempo médio de consulta, alta satisfação de pacientes e médicos, e considerável redução de custos.

Objetivo: Revisar a literatura sobre o custo-efetividade da telemedicina na neurologia e discutir os caminhos para sua regulamentação no sistema de saúde brasileiro.

Método: Esta revisão sistemática seguiu rigoroso processo metodológico. Foram utilizadas bases de dados como PubMed, Medline (BVS) e Science Direct. Os artigos foram filtrados com base na avaliação de pacientes através da teleneurologia e a análise dos custos e da efetividade desse serviço. Apenas estudos originais e ensaios clínicos em inglês ou espanhol foram incluídos, enquanto artigos duplicados e de revisão foram excluídos.

Resultado: Foram incluídos nesta revisão 29 artigos focados no tema.

Conclusão: A telemedicina na neurologia é custo-efetiva e oferece várias vantagens, como redução de custos, melhoria na qualidade de vida dos pacientes e maior acesso a especialistas e promissora para melhorar o atendimento em áreas rurais e remotas. No entanto, a regulamentação adequada, a padronização dos protocolos clínicos e técnicos, e a sustentabilidade financeira dos programas são essenciais para a sua implementação bem-sucedida. A evidência sugere que a teleneurologia pode e deve ser integrada nos principais serviços de saúde para otimizar o cuidado neurológico e reduzir disparidades no acesso ao tratamento.

PALAVRAS-CHAVE: Custo efetividade. Telemedicina. Teleneurologia.

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INTRODUCTION

The COVID-19 pandemic has increased the interest and practice of telemedicine among Brazilian neurologists. A survey conducted in 2020 showed that 56.2% of neurologists started working with telemedicine after the beginning of the pandemic, while only 18.5% worked with telemedicine before it.[1]

Such benefits can be measured by indicators such as the no-show rate, the average time spent in consultations, the satisfaction scale, and the effects on patients' health. Additionally, the average cost per virtual consultation was estimated to be $30, compared to $150 per face-to-face consultation. In addition[2], patient and physician satisfaction with virtual consultations, using a scale of 1 to 5, was high, with an average of 4.7, while physician satisfaction was similar, with an average of 4.5. Telemedicine can reduce healthcare costs by up to 20% by reducing hospital admissions, patient transfers, face-to-face consultations, and overdiagnosis.[3] An increase in the quality of life of patients by up to 30% was also noted by improving access to health services, reducing waiting times, avoiding commuting, and facilitating follow-up. Concomitantly, it improved the accuracy of the diagnosis of neurological diseases by up to 40% by allowing the evaluation of specialists at a distance, in addition to improving adherence to the treatment of neurological diseases by up to 50% by offering continuous support and guidance to patients.

In Europe, there is also evidence of the effectiveness and acceptance of telemedicine in neurology. In France4, its impact on the quality of neurological care in a rural region involved 12 general practitioners and 12 neurologists who carried out consultations by videoconference for 1 year. The study showed that teleneurology improved patient access to specialists, reduced waiting and travel times, increased patient and physician satisfaction, and did not compromise the quality of neurological care.

Thus, the objective of this review was to find evidence in the literature about the cost-effectiveness of telemedicine applied to neurology, as well as the ways to regulate this practice in the health service

METHOD

This article is a systematic review of the literature, a methodological analysis method that gathers evidence for clinical practice, through the search, evaluation and synthesis of available information on the specific topic to be analyzed. To carry out the present study, the following methodological steps were followed: identification of the theme and guiding question of the research; definition of inclusion and exclusion criteria; identification of the information to be extracted from the selected articles; analysis and interpretation of the results and presentation of the review. At first, the theme "Teleneurology and its cost-benefit for the health system" was established. Next, the guiding question was defined "Is teleneurology cost-effective enough to be regulated and used in the main health services in Brazil?". For scientific basis, searches were carried out in the PubMed, Medline (BVS) and Science Direct databases.

The articles were filtered in summary and included if they presented as a proposal the evaluation of patients through teleneurology, as well as the evaluation of the costs and effectiveness of this service. Based on this, articles that did not address the relationship between cost and benefits, that did not deal directly with patients treated by telemedicine, and studies that did not mention the regulation of teleneurology were excluded.

The search results were selected based on the exclusion and exclusion criteria that were applied to the articles made available in full. Only original studies related to the theme were included, focusing on clinical trials and randomized studies that answered the guiding question in English or Spanish. At the same time, duplicate articles, review articles, and those that did not fit the theme of this review were excluded.

DISCUSSION

A pilot randomized controlled trial in patients with Parkinson's disease showed that telemedicine can improve patients' quality of life and motor performance. Patients who received ongoing care via telemedicine had follow-up rates of up to 97%, and 13 of the 14 patients chose to receive more specialized care via telemedicine. Interobserver agreement in the remote assessment of patients with Parkinson's disease using telemedicine was excellent for postural stability, gait, and standing up from a chair; good for speech evaluation, facial expression, tremor at rest, hand and body bradykinesia; and fair for finger touches, hand grip and action shake. Remote stiffness assessment could not be performed as well.[1] The study presents a retrospective analysis of data on the implementation of a teleneurology network that was established to improve access to neurologists in rural areas and reduce the number of transfers of stroke patients to tertiary centers. During the 10-year study period, a total of 4296 stroke patients were evaluated through the teleneurology and telestroke network. Of these, 2493 were evaluated before the implementation of the teleneurology network and 1803 evaluated after its implementation. Patients evaluated before the implementation of the teleneurology network were older (66.4 years) compared to patients evaluated after (67.8 years). However, there were no significant differences in baseline characteristics between the 2 groups. The results showed that patients evaluated before the implementation of the teleneurology network were more likely to be transferred to the tertiary center (29.4%) compared to those evaluated after its implementation (20.2%). It was associated with significant reduction in stroke care costs, with an estimated average cost reduction of $4997 per patient.[2]

One study showed that telemedicine can reduce the waiting time for care for patients with neurological diseases by up to 50%. Another reported that it can reduce travel costs by up to 80% for patients living in remote areas. A systematic review study showed that telemedicine can improve the quality of care and patient satisfaction compared to face-to-face care. Another reported that telemedicine may be a viable option for the care of patients with Alzheimer's disease, especially for those who have mobility difficulties or live in remote areas. A systematic review highlighted the importance of evaluating the efficacy and effectiveness of telemedicine for the care of patients with neurological diseases, including Alzheimer's.[3]

According to Access 2022, a Canadian initiative to improve access to healthcare services, telemedicine can save up to $1.3 billion in healthcare costs per year. According to Canada Health Infoway, 77% of Canadian physicians reported using some form of digital health technology in 2018, a 14% increase from 2016. A 2017 Accenture report found that telemedicine could save up to $10 billion in healthcare costs in the United States. OTN, a Canadian telemedicine organization, reported that virtual visits can save up to 4 h of travel time for patients living in rural areas.[4] In question 5 of the questionnaire, 57.4% of neurologists answered that before the beginning of the COVID-19 pandemic they did not seek studies and scientific evidence in the areas of teleneurology and neurological examination through telemedicine, while 42.6% answered that they did. In question 6 of the questionnaire, 57.4% of neurologists answered that before the beginning of the COVID-19 pandemic they had not participated in face-to-face or online scientific event(s) on telemedicine or teleneurology, while 42.6% answered yes. In question 11 of the questionnaire, 56.2% of neurologists answered that after the beginning of the COVID-19 pandemic they started working with telemedicine, while 43.8% answered that they did not. The survey showed that 63.6% of neurologists said they worked with telemedicine during the pandemic, while only 18.5% worked with telemedicine before the pandemic.[5]

The article mentions that telemedicine can reduce stroke treatment time by up to 15 minutes, which can save up to 30 million neurons. The article mentions that telemedicine can increase access to neurology specialists in rural or remote areas, where the average ratio of neurologists per 100,000 inhabitants is only 0.033. The article reports that telemedicine can improve the quality of life of patients with Parkinson's disease, reducing face-to-face visits by 67% and transportation costs by 40%. The article states that telemedicine can facilitate the diagnosis and management of epilepsy, allowing electroencephalograms (EEGs) to be performed at a distance, with a sensitivity of 96% and specificity of 94%. The article concludes that telemedicine is a promising tool to improve the care of patients with neurological diseases, especially in remote or resource-scarce areas.[6]

> "The growing demand for neurological consultations around the world has driven the development of new ways to reach more patients. Telemedicine can provide accessible, low-cost, and high-quality health services." A growing body of evidence supports the feasibility and effectiveness of telemedicine tools for Parkinson's disease and other movement disorders." "Studies from different countries have shown that individuals with Parkinson's disease experienced worsening of motor and non-motor symptoms during the COVID-19 pandemic." "Telemedicine was considered an efficient and acceptable tool, technically feasible and satisfactory for patients, neurologists and nurses". "Telemonitoring, along with video conferencing, appears to be useful in identifying patients who may be candidates for advanced therapies for Parkinson's disease."[7]

Several studies have reported cost savings: teledermatology in Spain of 40% compared to conventional dermatology; telecardiology in Portugal of 50% compared to conventional cardiology; telepsychiatry in the USA of 24% compared to conventional psychiatry; telemedicine in oncology in Australia of 30% compared to conventional oncology.[8]

One study found that implementing a telemedicine program for stroke care in rural areas resulted in a significant reduction in the average time of care and in the number of patients transferred to larger hospitals. The average time of care was reduced from 120 to 45 min, and the number of patients transferred to larger hospitals was reduced from 50% to 10%.[9] The study indicates that telemedicine can help in the evaluation and treatment of headache, providing a 50% reduction in the frequency of crises and a 75% increase in patient satisfaction. The work shows that telemedicine can contribute to the care of patients with dementia, offering a 20% improvement in treatment adherence and a 30% decrease in depressive symptoms. The work reveals that telemedicine can optimize the diagnosis and therapy of sleep disorders, achieving 90% agreement between the results obtained at a distance and those performed in person.[10]

According to the authors, telestroke has been shown to improve access to and quality of care for stroke patients, reduce geographic and socioeconomic disparities, increase the use of evidence-based therapies such as intravenous alteplase and mechanical thrombectomy, and improve clinical and functional outcomes for patients. In addition, telestroke has been shown to be cost-effective from several perspectives, including that of the patient, the provider, the payer, and society. However, it also faces some challenges, such as the need to standardize clinical and technical protocols, ensure the quality and security of the data transmitted, adapt to ethical and legal standards, obtain medical licenses and accreditations in different states or countries, and adequately remunerate the services

provided. The financial sustainability of telestroke programs increased the use of intravenous alteplase from 2.6% to 15.5% in rural hospitals in the United States; it also reduced the average door-to-needle time from 80 min to 40 min in community hospitals in Germany. Telestroke improved the functional recovery of patients in 90 days, with a 14% reduction in mortality and a 25% reduction in dependence. It was cost-effective in different scenarios, with incremental cost-effectiveness ratios ranging from US$ 2,449 to US$ 4,569 per quality-adjusted life year.[11]

Regarding clinical effectiveness, 83% of studies found that telemedicine was at least as effective as face-to-face care, and some studies have shown that it can even improve patients' clinical outcomes. For example, one study compared the use of telemedicine to assess patients with suspected stroke in mobile emergency units with conventional care in hospitals. The study concluded that telemedicine reduced the average time between symptom onset and thrombolytic treatment from 94 min to 56 min, increasing patients' chances of recovery. Regarding cost-effectiveness, 39% of studies found that telemedicine was cost-effective or generated cost savings, while 28% found that it was cost-ineffective or increased costs. The other studies could not draw definitive conclusions on this aspect. The factors that influenced the cost-effectiveness of telemedicine were the type of intervention, the target population, the comparison scenario, the time horizon, and the perspective of the analysis. For example, one study compared the use of telemedicine to monitor patients with epilepsy with face-to-face care in specialized clinics. He said that telemedicine generated cost savings of US$ 278 per patient per year, considering the direct and indirect costs of the health system and patients. Regarding the patient experience, studies have reported high levels of acceptance and satisfaction with telemedicine, as well as benefits such as increased access, convenience, comfort, and autonomy. However, some patients have also expressed concerns about the quality, security, privacy, and confidentiality of the data, as well as the lack of in-person contact with healthcare providers. For example, a survey evaluated the perception of patients with Parkinson's disease about using telemedicine for regular consultations with neurologists and revealed that 97% of patients were satisfied with telemedicine and 86% preferred to continue using this method in the future. Patients also reported improvements in quality of life and treatment adherence. Regarding implementation, research has identified several facilitating factors and barriers to the use of telemedicine in clinical practice. Enabling factors included support from managers, professionals, and patients; the availability and adequacy of technological resources; integration with existing systems; and the qualification and training of those involved. Barriers included resistance to change; the lack of reimbursement or financial incentives; legal and ethical issues; the usability and reliability of the equipment; and the technical and organizational challenges. For example, one study analyzed the factors that influenced the implementation of teleneurology in different countries and found that teleneurology was more successful when there was clear demand, a sustainable business model, an engaged multidisciplinary team, adequate infrastructure, and favorable regulation.[12]

A multicenter study compared teleneurology with face-to-face neurology for the treatment of acute stroke in 11 rural hospitals in Bavaria, Germany. It showed that teleneurology was as effective as face-to-face neurology in evaluating patients, deciding on the use of tPA, the rate of bleeding complications, and 30-day mortality. A randomized study compared teleneurology with telephone neurology for the treatment of acute stroke in 6 rural hospitals in California, United States, and showed that teleneurology was superior to telephone neurology in the evaluation of patients, in the decision on the use of tPA, in the rate of tPA administration and in the functional outcome at 90 days. Retrospective research compared teleneurology with face-to-face neurology for the treatment of acute stroke in 2 urban hospitals in North Carolina, United States and showed that teleneurology was equivalent to face-to-face neurology in patient assessment, decision on tPA use, tPA administration rate, and functional outcome at 90 days. In addition, it also cites other studies that have shown the economic and social benefits of teleneurology for stroke, such as estimating the cost-effectiveness of teleneurology for stroke in the United States, considering the direct and indirect costs of telemedicine, tPA, and post-stroke care, which can generate savings of about $1,500 per patient treated, and a reduction of 0.02 quality-adjusted life years (QALY) lost per patient.[13]

Research on the video-consultation system for patients with multiple sclerosis estimated average savings of $2,824 per patient per year for the health system and average improvement of 0.02 QALYs per patient per year, and on the telemonitoring system in Parkinson's disease reported average savings of €2,017 per patient per year for the health system and average improvement of 0.03 QALYs per patient per year. As for the stroke telehealth system, it estimated average savings of $1,665 per patient per year and average improvement of 0.04 QALYs per patient per year.[14]

The average rate of non-attendance for virtual consultations was 5%, compared to 15% for face-to-face consultations. The average time spent by patients in virtual consultations was 30 min, compared to 90 min in face-to-face consultations. The average cost per virtual consultation was estimated at US$ 30, compared to US$ 150 in face-to-face. Patient satisfaction with virtual consultations was high, with an average of 4.[7] on a scale of 1 to 5. Physicians' satisfaction with virtual consultations was also high, averaging 4.[5] on a scale of 1 to 5. The authors recognize that there are some challenges and limitations for telemedicine in neurology, such as the

quality of the internet connection, data privacy, the training of professionals and patients, the adequacy of equipment and platforms, the validity of virtual neurological exams, and legal and ethical regulation. They suggest some measures to overcome these obstacles, such as the use of standardized protocols, the involvement of patients' caregivers, monitoring the quality of services, and collaboration between medical societies and government authorities.[15]

Telemedicine can reduce healthcare costs by up to 20% by reducing hospital admissions, patient transfers, face-to-face consultations, and unnecessary tests. It can increase patients' quality of life by up to 30% by improving access to health services, reducing waiting times, avoiding commuting, and facilitating follow-up. It can also improve the accuracy of diagnosing neurological diseases by up to 40% by enabling remote expert assessment and improve adherence to neurological disease treatment by up to 50% by providing ongoing support and guidance to patients. It can also reduce stroke mortality by up to 60% by speeding up emergency care and thrombolytic administration; increase satisfaction with health services by up to 70% by providing greater autonomy and participation in therapeutic decisions; increase healthcare professionals' job satisfaction by up to 80% by facilitating communication, collaboration, and continuing education.[16]

Telemedicine can reduce direct costs of care by up to 20% for ALS patients compared to in-person care; it can reduce indirect costs of care by up to $205 per visit, accounting for travel expenses, lost work time, and avoidable complications; it can increase operating costs by up to $150 per visit for providers, including expenses with equipment, training and maintenance; can improve patient satisfaction with care by up to 90%, compared to face-to-face care; improve treatment adherence by up to 75%, compared to face-to-face care; it can improve patients' quality of life by up to 0.07 points on the EQ-5D scale, which measures health status in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; can reduce the hospitalization rate by up to 50%, compared to face-to-face care17 and gained more QALYs with cost savings by 43% (6/14) and with higher cost than acceptable RICE by 57% (8/14). RICE amounts ranged between $2,700 and $68,000 per QALY earned. It reduced hospitalizations by 0.03 per patient per year in those with heart failure.[18]

The Victorian Stroke Telemedicine (VST) program implemented in 16 rural and regional hospitals in Australia between 2010 and 2018 consisted of a network of stroke specialists evaluating patients via videoconference and recommending the most appropriate treatment, including thrombolysis - administration of medication that dissolves blood clots. The paper uses retrospective observational data to estimate the costs and benefits of VST in terms of quality-adjusted life years (QALYs), a measure that combines duration and quality of life. It compared 2 scenarios: the baseline, which represented the usual care without the VST, and the intervention scenario representing the care with the VST. The results show that the VST was cost-effective, i.e., it generated more QALYs with acceptable cost per QALY gained. The incremental cost per QALY gained was $AUD 8,823 (about R$ 34,000.00) in the base scenario, and $AUD 5,988 (about R$ 23,000.00) in the intervention scenario. It was also cost-effective, that is, it generated more benefits than costs. The net benefit of VST was $AUD 2,835 (about R$ 11,000.00) per patient in the base scenario, and $AUD 3,835 (about R$ 15,000.00) in the intervention scenario.[19]

Telemedicine is an alternative that can increase the use of cardiac rehabilitation (CR), especially for patients who have difficulties accessing or adhering to face-to-face programs. The authors conducted a systematic review of 12 randomized controlled trials that compared telemedicine CR with exercise-based CR performed in specialized centers (CBCR) in patients with heart disease. Most studies (92%) found strong evidence that telemedicine CR is cost-effective. Compared with CBCR, there were no significant differences, except in three studies that evaluated a significant difference in the average cost per patient and in the costs of the intervention in favor of CR by telemedicine. The costs related to patient transportation and absence from work were lower for patients who participated in CR by telemedicine than for those who participated in CBCR. The average costs per patient ranged from €127 to €2,691 for telemedicine CR and from €408 to €3,298 for CBCR. The costs of the intervention ranged from €0.6 to €1,500 for CR by telemedicine and from €0.8 to €2,000 for CBCR. Absence from work ranged from €0 to €607 for CR by telemedicine and from €0 to €2,691 for CBCR. Transport ranged from €0 to €82 for RC by telemedicine and from €0 to €408 for CBCR.[20]

Telemedicine can reduce healthcare costs associated with diabetes, which account for about 12% of global healthcare spending. The incremental cost-effectiveness ratio (CSI) is a measure that compares the additional costs and benefits of one intervention in relation to another. The lower the ICER, the more cost-effective the intervention. The use of telemedicine for retinal screening was beneficial and cost-effective for the management of diabetes, with an ICER between $113.48/QALY and $3,328.46/QALY (adjusted for 2017 inflation). This means that telemedicine can generate a quality-adjusted life year (QALY) at an additional cost of between $113.48 and $3,328.46 compared to usual care. In R$, this is equivalent to between R$ 607.76/QALY and R$ 17,817.90/QALY, using the average exchange rate of 2023 (R$ 5.35/US$). The use of telemonitoring and telephone reminders was also cost-effective in the management of diabetes. The ICER for telemonitoring ranged from $2,280/QALY to $68,463/QALY, while that for phone reminders ranged from $1,837/QALY to $13,638/QALY. In R$, this is equivalent to the additional cost between R$12,198.00/QALY

and R$366,378.00/QALY for telemonitoring, and between R$9,838.00/QALY and R$72,964.00/QALY for telephone reminders. Among all the telemedicine strategies examined, teleophthalmology was the most cost-effective. It is the use of technology to provide eye care services at a distance, such as retinal tracking to prevent or treat eye complications from diabetes. Most studies were conducted in high-income countries, which limits the applicability of the findings to low- and middle-income countries, where access to and quality of diabetes care may differ.[21]

Outcomes after treatment with intravenous tissue plasminogen activator via telemedicine (telestroke) are similar to those obtained with face-to-face assessments. Telemedicine allows neurological expertise to be delivered to remote locations to complement or replace in-person neurological care and can improve access to specialized neurology services for patients around the world. Treatment with tissue plasminogen activator via telemedicine is a way to offer rapid and effective thrombolytic therapy to patients with acute ischemic stroke who do not have access to a specialized center. The treatment consists of evaluating the patient through videoconferencing with a neurologist, who can prescribe the drug and monitor its effect. The drug is administered by trained local staff, who follow the neurologist's instructions from a distance. The goal is to dissolve the clot that is obstructing blood flow to the brain and restore neurological function.[22]

After the implementation of telemedicine, a rural hospital was able to reduce the average time between patient arrival and thrombolytic administration from 120 min to 60 min, reaching the goal set by the American Stroke Association. In addition, it increased the thrombolytic administration rate from 0% to 15%, above the national average of 10%. Telemedicine also brought financial benefits to the rural hospital, which started to receive additional remuneration for each stroke patient treated. The annual cost of telemedicine was estimated to be $36,000, while the revenue generated was $108,000, resulting in a return on investment of 200%.[23]

The use of virtual visits reduced in-person visits by 33% but increased total visits (virtual plus in-person) by 80% over 1.[5] years. Patients who used virtual visits were younger, more likely to be men, had fewer comorbidities, and lived farther away from the doctor's office than those who did not use virtual visits. Those who used it reported high satisfaction with the program and there was no difference in the quality of care between virtual and face-to-face care. 24-27

Utilization and cost-effectiveness of telemedicine program in western regions of China between 2004 and 2015 treated 1,210,571 patients, of whom 1,036,571 (85.6%) had stroke. The control group consisted of 1,210,571 patients treated in person, of whom 1,036,571 (85.6%) had stroke. The telemedicine program in neurology significantly reduced the mortality rate from stroke (from 8.9% to 5.2%), the severe disability rate (from 32.8% to 19.2%), and the average length of hospital stay (from 15.2 days to 9.4 days) with an average cost per patient (from ¥3,562 to ¥2,279).[28]

Neurological telemedicine as a form of intervention in Parkinson's disease

A pilot randomized controlled trial in patients with Parkinson's disease showed that teleneurology can improve patients' quality of life and motor performance, as patients who received continuous care via telemedicine had follow-up rates of up to 97%, and 13 of the 14 patients chose to receive more specialized care via telemedicine. There is also the mention that there was an improvement in the quality of life of patients with Parkinson's disease, reducing face-to-face visits by 67% and transportation costs by 40%. In addition, a growing body of evidence supports the feasibility and efficacy of telemedicine tools for Parkinson's disease and other movement disorders, given that different countries have demonstrated that individuals with Parkinson's experienced worsening of motor and non-motor symptoms during the COVID-19 pandemic. In this way, telemonitoring, along with videoconferencing, could be useful in identifying patients who may become candidates for advanced therapies for Parkinson's disease. For example, one study evaluated Parkinson's patients' perception of using telemedicine for regular consultations with neurologists. It was revealed that 97% were satisfied and 86% preferred to continue using this method in the future. Improvements in quality of life and treatment adherence have also been reported. In addition, a report on the telemonitoring system in Parkinson's estimated an average saving of € 2,017 per patient per year for the health system and an average improvement of 0.03 QALYs (quality-adjusted life year) per patient per year.[29]

The role of teleneurology in other neurological conditions

Telemedicine can facilitate the diagnosis and management of epilepsy, allowing remote electroencephalograms, with a sensitivity of 96% and specificity of 94%. In addition, other studies indicate that it can help in the evaluation and treatment of headache, providing a 50% reduction in the frequency of crises and a 75% increase in satisfaction. It has been shown that it can contribute to the care of patients with dementia, offering a 20% improvement in treatment adherence and a 30% decrease in depressive symptoms. In addition, another article revealed that it can optimize the diagnosis and therapy of sleep disorders, achieving 90% agreement between the results obtained at a distance and those in person. In addition, there are studies that evaluate the economic impact of teleneurology, showing that this modality can generate significant savings for the health system and patients, given that in epilepsy it was estimated that it generated savings of $278 per patient per year, considering the direct and indirect costs of the health system. Video consultation for MS

patients has already been shown to deliver average savings of $2,824 per patient per year to the healthcare system and average improvement of 0.02 QALYs per patient per year; It has also been realized that it can reduce the overhead costs of care by up to $205 per visit for patients with amyotrophic lateral sclerosis, considering travel expenses, lost work time, and avoidable complications.[29]

Teleneurology and its limitations

Although it presents itself as promising, telemedicine in neurology also faces some limitations and challenges for its development and dissemination. A study listed the main challenges reported, which would be: the lack of adequate technological infrastructure, which enables a stable and secure connection between the patient and the doctor, as well as the transmission of reliable clinical data; the lack of legal and ethical regulation, which defines the rights and duties of professionals and patients involved in telemedicine, as well as the rules of privacy and confidentiality of data; the lack of professional training, which prepares doctors and health teams to use telemedicine tools efficiently and with quality, in addition to developing communication and empathy skills at a distance; the lack of acceptance and adherence of patients, who may have difficulties or resistance to use telemedicine, whether for cultural, educational or socioeconomic reasons. In addition, a study conducted by the American Academy of Neurology reported that the main challenges reported by neurologists who used telemedicine were patients' lack of access to the proper technology (69%), difficulty in performing neurological exams (67%), concerns about data privacy (45%), and lack of adequate reimbursement (43%).[29]

CONCLUSION

The advances achieved by teleneurology have stimulated technological innovations that, when incorporated into health processes, have created opportunities to improve the care provided to patients treated through this system. Thus, understanding that the present review is not enough to give the final verdict on telemedicine, there is a need to search for strategies that guarantee this reliability and clinical studies that prove these ideas.

Authors' contributions

Guilherme Nobre Nogueira: Project administration
Hugo Lorran Souza Costa: Validation, Writing – review & editing
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Hippocampal plasticity induced by physical activity: an integrative review

Plasticidade hipocampal induzida pela atividade física: uma revisão integrativa

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ABSTRACT

Introduction: The hippocampus can be influenced by the regular practice of physical exercise e, which can be used as a non-pharmacological treatment for both physiological and pathological cognitive disorders.

Objective: To understand the influence of physical exercise on the plasticity and development of the hippocampus.

Method: Integrative review on the most recent advances in this field of study. The descriptors were "Resistance exercise", "Plasticity" and "Hippocampus".

Results: In a total, 23 articles were analyzed, from which 9 were chosen due to their relevance.

Conclusion: Physical activity affects hippocampal plasticity, as well as it helps regulate humor and maintain cognition, due to various mechanisms, such as hormonal homeostasis regulation and the increase of synaptic efficiency. Physical activities are an important external modulator of hippocampal plasticity, with a possible therapeutic effect on protecting the nervous system against cerebral degeneration caused by aging and neurodegenerative diseases.

KEYWORDS: Exercise. Resistance exercise. Neurogenesis. Neurology.

RESUMO

Introdução: O hipocampo pode ser influenciado pela prática regular de exercício físico e, que pode ser utilizado como tratamento não farmacológico tanto para distúrbios cognitivos fisiológicos quanto patológicos.

Objetivo: Compreender a influência do exercício físico na plasticidade e desenvolvimento do hipocampo.

Método: Revisão integrativa sobre os avanços mais recentes neste campo de estudo. Os descritores foram "Exercício resistido", "Plasticidade" e "Hipocampo".

Resultados: No total, foram analisados 23 artigos, dos quais 9 foram escolhidos devido à sua relevância.

Conclusão: A atividade física afeta a plasticidade hipocampal, bem como ajuda a regular o humor e manter a cognição, devido a vários mecanismos, como a regulação da homeostase hormonal e o aumento da eficiência sináptica. As atividades físicas são um importante modulador externo da plasticidade hipocampal, com possível efeito terapêutico na proteção do sistema nervoso contra a degeneração cerebral causada pelo envelhecimento e doenças neurodegenerativas.

PALAVRAS-CHAVE: Exercício. Exercício resistido. Neurogênese. Neurologia.

Central Message

Physical activity has a significant impact on hippocampal plasticity, especially through interaction with hormonal and vascular factors. The article discusses how exercise, at different intensities and types, can influence neuroplastic processes such as neurogenesis, angiogenesis and the expression of neurotrophic factors, contributing to the regulation of mood and cognition. However, it also highlights that the intensity and nature (forced or voluntary) of exercise can generate stressor effects that, in some cases, attenuate the neuroplastic benefits.

Perspective

Physical exercise, especially moderate-intensity exercise, may be a crucial behavioral intervention to maintain brain plasticity throughout life, potentially offsetting the effects of aging and stress. Furthermore, controversies regarding responses to exercise are highlighted, highlighting the importance of variables such as sex, intensity, and duration of exercise in modulating these effects.

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INTRODUCTION

The hippocampus is a discrete but important telencephalic structure, located in the medial zone of the temporal lobe. It is necessary for spatial and episodic memory[1], besides being related to the ability of learning.[2] Furthermore, it is also related to an individual's stress response.[3] The two main anatomical divisions of the hippocampal structure are respectively called Ammon's horn and dentate gyrus. Ammon's horn can be subdivided in zones from CA1 to CA4, whilst the dentate gyrus is a big neurogenesis area in adult brains.[4]

In terms of functional division, the hippocampus is subdivided according to its longitudinal axis in 2 different areas: dorsal or septal zone, which plays a role in memory and spatial information, sending outputs to the anterior cingulate cortex, anterior thalamus and mammillary body. Regardless, the temporal zone of the hippocampus is mostly related to the sense of smell, the prefrontal cortex and the amygdala, managing stress response.[5]

Knowing all these functions, the hippocampal structure can be influenced by various factors. The genetic factor can be determined by the individual's sex, which determines the production of androgen hormones (testosterone and its metabolites) or estrogens (like estradiol), both of those being responsible for subtle differences in hippocampal structure. Changes not related to genetics include post-traumatic stress disorder and the individual's lifestyle.[6]

This article approaches the influence of regular exercise practice in the development (plasticity) of the hippocampus, based on various studies, both in animal and human models, about the maintenance of the structural and functional integrity of the hippocampus, therefore, having it as a non-pharmacological treatment for cognitive deficits, in both physiological and pathological conditions, such as, respectively, aging and Alzheimer's.

METHOD

This is an integrative review, which was researched through the use of DeCS/MeSH descriptors "Resistance exercise", "Plasticity" and "Hippocampus", crossed with "AND" and "OR' Boolean operators for searching on the ScienceDirect database. The chosen period was from 2011 to 2023. This way, 130 articles were found according to the inclusion criteria: English language, publishing period, and research articles (clinical trials, cohort studies, cross-sectional studies, case reports) and experimental studies) and relevant information about the guiding question, with a total of 23 articles being analyzed, from which 9 were chosen to compose this revision; The exclusion criteria for the non-selected articles were based on works that did not align with the article's theme or review articles.

DISCUSSION

At first, 23 articles of higher academic relevance for the study of the present theme were analyzed, from which 9 stood out, being later selected for the final review presented in this study. For the presentation of those, Table 1 appears with its fundamental characteristics.

Table categorizes the used articles, presenting their title, writer, base, publishing year, country of origin and where it was first published. Also in this table are listed the objectives and conclusions presented in each analyzed article. This way, the various reviewed studies describe the characteristics of hippocampal plasticity in its relation to physical activity in humans and lab species, noticeably small rodents, which are used in 6 out of the 9 articles described.

Therefore, the articles present the same theme in various different approaches, in a way to constitute a plural integrative review about exercise induced hippocampal plasticity.

Age, hormonal homeostasis and physical activity level are some of the factors that impact hippocampal plasticity, but the exact mechanisms through which these factors interact with each other in specific moments are not yet comprehended.[7,8]

The perspective of development throughout life's course shows that the biological incorporation of experiences that happened during early childhood continues for the years ahead, as well as the concept that physical and social conditions continuously change the brain and the body through epigenetics. This dynamic interaction gives the possibility of redirecting towards a better path through behavior interventions, like physical activity, that open plasticity windows.[9,10]

In a study with rats, it was observed an association between circling Insulin-like Growth Factor 1 (IGF-1) and physical aptitude in teenage individuals. IGF-1 is predominantly synthesized in the periphery, and later on crosses the hematoencephalic barrier, unleashing the release of serial growth factors, those which result in effects on neural development. With that, it was verified an increase in the Vascular Endothelial Growth Factor (VEGF) after physical training, with the interaction between VEGF and IGF-1 showing a promotion in neurogenesis and angiogenesis.[11]

Therefore, it is important to highlight that it is already foreseen in literature that physical activity can generate indirect effects over hippocampal plasticity, by influencing mostly brain vascular factors, with blood flow and new vase generation that may contribute to possible alterations in this mechanism.[12]

By analyzing the effects of physical exercise in hippocampal plasticity in experiments with rats, it is noted that there is a vast study about inherent variables of the study object, such as sex, and variables inherent to physical exercise, whether these are voluntary or forced, if the exercises are implemented in short or long term and whether they are low, medium or high intensity.[7,11,12]

One of the main highlighted points is that both forced physical exercise (in comparison to voluntary exercise) and high intensity physical exercise (compared to low and medium intensity ones) may result in stressing effects in rodents, such as the increase in toxic substances in this context, like corticosterone and lactate, which relate to the decrease in potential beneficial effects of exercise over hippocampal plasticity. Regardless, it is fundamental to say that there are controversies on this matter, one of them being that the reactions to stressing effects can be managed.[13,14]

Another important parameter is whether exercise is done in short or long term, that being about how long they last. On this matter, one of the most important points is how the duration of these exercises affect the different phases of neurogenesis e how they affect the expression of specific factors related to hippocampal plasticity, such as the expression of BNDF and NGF.[15,16]

Still on this matter, it is relevant to say that short periods of physical exercise can generate significant results on abilities related to memory, if associated with a posterior reactivation of this previous stimulus. That can be seen in a study in which female mice were divided into groups and submitted to an object location memory test (OLM), during different periods. In this study, an experimental group did voluntary exercises for 14 days (short term), followed by a period of inactivity of 7 days a period of voluntary physical activity of 2 days, and presented superior results in the OLM in comparison to the group that did only the 14 days of exercise and the 7 days of inactivity, without the 2 days of returning to physical activity.[7]

It is recurrent the information that in female and male rodents there are differences in the effects of exercise over neural plasticity, justified by many hormonal and hippocampal structural factors, with an emphasis on the influence of estrogen on the levels of proteins related to hippocampal plasticity, as the BNDF.[7] The study in female rodents previously cited also evaluated the possibility of having different results in the OLM and the amount of physical activity according to the estrous cycle, which presents periods of variable female hormone levels. But, it was noted that regardless of different levels of voluntary physical activity being observed in rodents in different phases of the estrous cycle, their outcome in the OLM didn't show notorious differences, even if the study was limited by its small sample size.[7]

Regardless of these studies limitations, the difference in the effects of physical activity between sexes was also noted in another experiment with rodents, in which it was verified an increase in anxiety levels in females after being forced to exercises in a running mill, whilst there were no alterations in the males, which helps the thesis that physical activity affects opposite sex animals differently.[11]

In this same study, it was seen that beyond the countless benefits, forced physical training can also unleash negative stress and increase behaviors similar to anxiety, with high levels of corticosterone being registered after sessions of forced training in running mills. It has been frequently observed that the forced training protocols stimulate the release of glucocorticoids and affect the regulation of the negative feedback cycle, mediated by glucocorticoid receptors (GRs), portraying a determinant role in the response modulation in the hypothalamus-hipofisis-adrenal axis (HHA). Consequently, the increased presence of glucocorticoids may reduce the expression of GRs and affect the levels of BDNF.[11]

Furthermore, it was verified that even though in

TABLE— Characterization of the articles selected (n = 9)[7-9,10-15,17]

N° / Author, Year	Title	Journal	Objectives	CONCLUSION
1- Dong et al., 2022[7]	(Animal study) Temporal endurance of exercise-induced benefits on hippocampus-dependent memory and synaptic plasticity in female mice	Neurobiology of Learning and Memory	Examine the necessary parameters in the temporality of physical exercise in a way to initiate and maintain the cognitive benefits of these practices in female mice.	The benefits induced by physical exercise have a temporal dynamicity in female mice due to hormonal cycles.
2- Rostami et al., 2021[11]	(Animal study) The downstream effects of forced exercise training and voluntary physical activity in an enriched environment on hippocampal plasticity in preadolescent rats	Brain Research	Evaluate the effects of high intensity physical exercise in brain function during the pre-puberty period in rats and the impacts of ambiental cognitive stimuli concomitant to this practice.	When not accompanied by ambiental cognitive stimuli, high intensity physical activity may have a negative impact on hippocampal plasticity by hormonal effects related to stress and anxious behavior.
3- Broadhous EA et al., 2020[10]	(Clinical Trial) Hippocampal plasticity underpins long-term cognitive gains from resistance exercise in MCI	NeuroImage: Clinical	Investigate the long-term impacts of resistance physical exercise on cerebral structure and cognition, focusing on the impacts of this practice on neuroprotection against hippocampal aging and the degeneration of Alzheimer's disease.	The findings emphasize the potential therapeutic role of physical activity in hippocampal protection for up to 1 year after finishing medium and high intensity exercise. Besides that, they demonstrate a protective role over hippocampal subareas susceptible to volume loss due to Alzheimer's disease.
4- Ávila-gámiz et al., 2023[17]	(Animal study) Sequential treadmill exercise and cognitive training synergistically increase adult hippocampal neurogenesis in mice	Physiology & Behavior	Evaluate if male mice subjected to exercise in a mechanical running combined with cognitive training have a higher benefit on hippocampal neurogenesis if compared to any other individualized treatments.	The cell proliferation on the hippocampus of adult mice requires a lesser than 10 days limit of medium intensity running to elevate the performance of spatial memory. When this practice is combined with cognitive stimulation, a bigger plasticity on the dentate gyrus is noted.
5- Triviño-paredes et al., 2016[12]	The effects of hormones and physical exercise on hippocampal structural plasticity	Frontiers in Neuroendocrinology	Describe the impact of internal modulators (hormones) and external (physical activity) on hippocampal plasticity in human adults, highlighting the specific molecular mechanisms involved in this brain phenomenon.	The hippocampus is one of the few regions in adults that has as much synaptic plasticity as structural plasticity, and many of the effects of physical activity on this region of the brain are regulated by hormonal action, which is explained by the high amount of systemic hormonal receptors in the hippocampus.
6- Constans et al., 2020[15]	(Animal study) High-intensity interval training is superior to moderate intensity training on aerobic capacity in rats: Impact on hippocampal plasticity markers	Behavioural Brain Research	Compare the impacts of high intensity physical training alternated with medium intensity ones over the muscular performance and brain plasticity of healthy rats for 8 weeks.	Periodic high intensity physical training can bring more benefits to the hippocampal structure than continuous medium intensity exercises, but neither of those present cognitive benefits over spatial memory.
7- De Senna et al., 2016[14]	(Animal study) Physical exercise reverses spatial memory deficit and induces hippocampal astrocyte plasticity in diabetic rats	Brain Research	Investigate the effects of physical activity on the prevention of cognitive deficits induced by type 1 mellitus diabetes on the hippocampal region's astrocytes.	Physical exercise can induce a higher brain plasticity, reducing and reverting spatial memory deficits caused by type 1 mellitus diabetes.
8- Liu et al., 2017[9]	(Animal study) Swimming exercise reverses CUMS-induced changes in depression-like behaviors and hippocampal plasticity-related proteins	Journal of Affective Disorders	Comprehend the molecular mechanisms of mild and unpredictable chronic stress signalizing over the protein expressions related to hippocampal plasticity.	Chronic stress harms the expression of proteins like GAP-43 and synaptophysin
9- Ferreira et al., 2011[13]	(Animal study) Short-term, moderate exercise is capable of inducing structural, bdnf-independent hippocampal plasticity	Brain Research	Investigate the short term and moderate intensity benefits of physical activity in adult male rats, through immunohistochemistry studies, genetic studies and western blotting.	Physical exercise induces an improvement of hippocampal plasticity, which promotes cognitive benefits in short term through regulation of proteins related to mitochondrial metabolism, as well as long term, since the neurotrophic factors produced protect the hippocampal neurons linked to glutamatergic excitotoxic action.

3 weeks of combined physical exercise there was a significant increase of GR proteins in the hippocampus, there was no impact in the blood levels of corticosterone on the studied rodents. These results may be related to the adaptation of the HHA axis to appropriate stress. Is supposed that the stress response activation relies on the intensity of the physical training, but this hypothesis is not well defined in literature. On the other hand, the rats exposed to a stimulus enriched environment (SEE), which included a large cage and a variety of stimulant objects (balls, seesaws, tunnels and toys to promote cognitive abilities, as well as an exercise wheel and many ladders for exercising), showed a significant increase in GRs, alongside a decrease in blood levels of corticosterone. These discoveries showcase evidences that the AEE seems to reduce activity in the HHA axis. That being, social interaction, voluntary physical activity and pleasure may as well contribute to the reduction of activity in the HHA axis.[11]

Physical exercise, specially of moderate intensity, with emphasis on cardiovascular training, are crucial to maintain homeostasis.[13] Also, it was proved that high intensity and long duration resistance training is an effective form of exercise to reduce dysfunctions caused by diabetes, such as endothelial damage and neuropathies.[14]

In another study with rodents, it was verified that High Intensity Interval Training (HIIT), when compared to medium intensity continuous training (MICT) during a period of 8 weeks revealed higher levels of markers in the hippocampus associated to synaptic plasticity, neurogenesis and angiogenesis, but there are still controversies in academic literature about the comparison of different physical exercise regimens in studies with rodents due to methodological inconsistencies. In this same study, cognitive tests were applied, such as the y maze test and the object recognition test, but in neither of the isolated training modalities were found significant differences comparing the first and fifty-seventh day.[15] On the other hand, low intensity exercises also have an important role in rodents with neurological lesions. That can be seen in cases of male rats which were brain stroke models, that after being submitted to 4 weeks of low intensity exercise showcased an improvement in abilities related to the hippocampus of object recognition when compared to the rodents that spent the same 4 weeks doing high intensity exercises.[16]

In this context, it is seen that hormonal modulation may be one of the various mechanisms through which physical activity positively affects not only hippocampal plasticity but also cognition and mood regulation.[16]

Exercise induces synaptic plasticity of the hippocampus mainly through the improvement of the synaptic efficiency and the expression of molecules involved in learning and memory. An increase in neurotrophic factors, such as the brain derived neurotrophic factor (BDNF), the neural growth factor (NGF), the fibroblast growth factor (FGF) and their mRNAs were broadly noted after exercise. These factors promote neuroprotection against the excitotoxic effects of glutamate in cell cultures.[13] In studies with diabetic rodents, it was observed that physical exercise did not have a significant impact on body weight, blood glucose levels or glucose capture in the hippocampus. Nonetheless, it was noted that physical training was efficient in reverting the memory deficits induced by type 1 diabetes. This finding may be related to improvement in parameters such as neural plasticity in the hippocampus, long term potentiation, astrocyte proliferation, neurogenesis, reduction of oxidative stress (through the increase in hippocampal levels of GSH) and astrocyte plasticity.[16]

Furthermore, in another study it was verified that there is a synergism in the hippocampal neurogenesis in adult rats with the sequential combination of physical activity and hippocampal-dependant memory training. In addition to that, it was verified through Morris water maze that the rodents that exercised were more efficient in task solving and showed a better capacity of retaining information. The success in maze training may have been due to additional neurocognitive resources derived from physical stimulus, correlating changes in the processing and controlling of hippocampal neurogenesis to physical activity.

On a different view, the loss of protection of brain plasticity, which can be induced by stress, may contribute to the emergence and recurrence of depression. It was related that chronic stress opens epigenetic plasticity windows in the hippocampus.[9]

CONCLUSION

The factors that modulate the beneficial relation between physical activity and synaptic and structural plasticity in the hippocampus are various, from which can be stood out age, sex, stress level, duration and intensity of training and presence of external cognitive stimuli. Most of physical exercise's modulating effects over hippocampal neurogenesis are mediated through systemic hormones, which have high variations through people's lives, then being physical activity a possible therapeutic measure to maintain a healthy hormonal balance in each different stage of life. Besides that, sex hormones also show clinical influence in synaptic plasticity in female sex individuals, due to the natural estrogen variation during the menstrual cycle and the intrinsic role of this hormone over brain derived neurotrophic factors expression modulation in the hippocampus. Physical activity also promote positive effects over hippocampal cognition through the prevention of moderate unpredictable chronic stress in people, since this clinical condition harms the expression of synaptic plasticity modulator proteins, such as GAP-43 and synaptophysin (SYP), in the CA1 and dentate gyrus hippocampal regions. Furthermore, the frequency and intensity of physical exercise, on their own, promote distinct effects over hippocampal plasticity and spatial memory linked to this structure, since medium and high intensity trainings are related in various studies to the increase of molecular markers of brain plasticity, like glial fibrillary acidic protein (GFAP), NGF e SYP , as long as it happens within a minimum time between 10 and 14 consecutive days. According to the studies compiled in the extension of this article, physical activity

is an important extrinsic modulator of hippocampal plasticity, performing a possible therapeutic role on neural protection against brain degeneration induced by aging and by neurodegenerative diseases such as Alzheimer's, besides acting in reverting spatial memory deficits induced by previous pathologies, like type 1 mellitus diabetes. Having all of this in mind, this article still has a notable deficit in the number of studied samples when noting the high amount of existing relevant research on this topic. Therefore, more complex and extensive studies about hippocampal plasticity induced by physical exercise are needed.

Author´s contribution

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What differences lymphoma from vestibular schwannoma?

O que diferencia o linfoma do schwannoma vestibular?

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ABSTRACT

Introduction: Vestibular schwannoma (VS) is a benign tumor originating in the Schwann cells surrounding the vestibular nerve. Its initial symptoms include progressive hearing loss in one ear, representing an intracranial threat due to the mass effect. On the other hand, cerebral lymphomas, although rare, present with a variety of focal and non-focal neurological symptoms. The association of rapidly progressive unilateral hearing loss, tinnitus and vestibular dysfunction suggests VS.

Objective: To search for cases of lymphoma mimicry in relation to vestibular schwannoma, to describe the differential diagnosis and events associated with it.

Method: Integrative review conducted with methodological rigor, gathering evidence for clinical practice. It was performed in the PubMed and Medline databases, using the Boolean operator "AND" to associate relevant descriptors.

Result: Of the 96 articles found, 8 were selected based on the guiding question. Original studies in English or Spanish were included. Early diagnosis of VS is based on magnetic resonance imaging and hearing tests. Radiotherapy is a viable alternative. Furthermore, intracanalicular lesions of the internal auditory nerve are frequently VSs, but differential diagnoses should consider other possibilities, such as facial neuroma. The radiological features of VSs are not specific, and differential diagnoses need to be considered.

Conclusion: Differentiating lymphomas located in the cerebellopontine angle from VSs is crucial to avoid inappropriate treatments. Radiosurgery proposed for presumed small VSss may be inappropriate if the diagnosis is another one, such as lymphoma. Therefore, it is essential to obtain an accurate histopathological diagnosis to guide appropriate treatment.

KEYWORDS: Lymphoma. Auditory nerve. Acoustic neuroma. Vestibular schwannoma.

Central Message

The article explores the differential diagnosis between vestibular schwannoma and intracranial lymphoma, highlighting the clinical and radiological similarities that can lead to misdiagnosis. Accurate identification of these conditions is essential to ensure correct treatment, avoiding inappropriate interventions, such as radiosurgery in cases of lymphoma.

Perspective

The review reinforces the importance of early differentiation between vestibular schwannoma and lymphoma, using advanced imaging techniques and collaboration with neuroradiologists. The article highlights that inaccurate diagnoses can result in inaccurate treatments, underlining the need for rigor in the diagnostic process.

RESUMO

Introdução: O schwannoma vestibular (SV) é tumor benigno originado nas células de Schwann que circundam o nervo vestibular. Seus sintomas iniciais incluem perda auditiva progressiva em um dos ouvidos, representando ameaça intracraniana pelo efeito de massa. Por outro lado, os linfomas cerebrais, embora raros, apresentam-se com variedade de sintomas neurológicos focais e não focais. A associação de perda auditiva unilateral rapidamente progressiva, zumbido e disfunção vestibular sugere SV.

Objetivo: Buscar casos de mimetismo de linfomas em relação ao schwannoma vestibular, para descrever o diagnóstico diferencial e os eventos associados a ele.

Método: Revisão integrativa conduzida com rigor metodológico, reunindo evidências para a prática clínica. Foi realizada nas bases de dados PubMed e Medline, utilizando o operador booleano "AND" para associar descritores relevantes.

Resultado: Dos 96 artigos encontrados, 8 foram selecionados com base na questão norteadora. Foram incluídos estudos originais em inglês ou espanhol. O diagnóstico precoce do SV baseia-se em ressonância magnética e testes auditivos. A radioterapia é alternativa viável. Além disso, lesões intracanaliculares do nervo auditivo interno são frequentemente SVs, mas diagnósticos diferenciais devem considerar outras possibilidades, como neuroma facial. As características radiológicas do SV não são específicas, e diagnósticos diferenciais precisam ser considerados.

Conclusão: Diferenciar linfomas localizados no ângulo pontocerebelar de SV é crucial para evitar tratamentos inadequados. A radiocirurgia proposta para supostos SVs pequenos pode ser inapropriada se o diagnóstico for outro, como um linfoma. Assim, é fundamental obter diagnóstico histopatológico preciso para orientar o tratamento adequado.

PALAVRAS-CHAVE: Linfoma. Nervo auditivo. Neuroma acústico. Schwannoma vestibular.

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INTRODUCTION

Vestibular schwannoma (VS) is a benign tumor that originates in the cells surrounding the vestibular nerve (Schwann cells). Initial symptoms, as the tumor grows and presses on the auditory nerve, include progressive hearing loss in one ear. It poses a threat to intracranial structures due to the mass effect and presents a small risk of malignant transformation.[1]

Regarding lymphomas, the incidence varies from 0.[4] to 0.5 per 100,000 inhabitants per year, corresponding to less than 1% of all non-Hodgkin's lymphomas and 3% of all brain malignancies. Presents with focal neurologic deficits (70–73%), neuropsychiatric symptoms (28–43%), seizures (9–14%), ocular symptoms (4%), and increased intracranial pressure (3–33%). Most lymphomas are supratentorial and localized intra-axially. Most supratentorial lesions occur in the cerebral white matter or corpus callosum, some in the deep central gray nucleus, the posterior fossa, and rarely in the spinal cord.[2]

The association of rapidly progressive unilateral hearing loss, tinnitus, and vestibular dysfunction in combination with a contrast-enhanced mass within the internal auditory canal on magnetic resonance imaging (MRI) suggests VS.[3] In this sense, the scope of the present review was to search the literature for cases of lymphoma mimicry in relation to VS, in order to describe the differential diagnosis and the events associated with this distinction.

METHOD

This article is an integrative literature review, a methodical analysis method that gathers evidence for clinical practice, through search, evaluation and synthesis of available information on the specific topic to be analyzed. To carry out the present study, the following methodological steps were followed: identification of the theme and guiding question of the research; definition of inclusion and exclusion criteria; identification of the information to be extracted from the selected articles; analysis and interpretation of the results and presentation of the review.

At first, the theme "vestibular schwannoma and its neurosurgical approaches" was established. Next, the guiding question was defined: "How can lymphoma mimic a vestibular schwannoma?".

For scientific basis, searches were carried out in the PubMed and Medline databases, using the Boolean operator "AND" to associate the descriptors in the search.

Of the 96 articles found, 7 were chosen with a view to reading the article and selection based on relevant aspects of the guiding question, series and case reports on lymphomas mimicking VS were chosen to compose the present review.

Only original studies related to the theme that answered the guiding question in English or Spanish were included. At the same time, duplicate articles, review articles, and those that do not fit the theme of the present review were excluded, resulting in 36 articles in Pubmed and 46 in Medline.

DISCUSSION

Early diagnosis of VS is based on MRI and hearing tests. It is usually unilateral but may be bilateral in neurofibromatosis type 2. In addition, there are several surgical techniques to remove VS, the most common being translabyrinthine and rectosigmoid approaches. Due to surgical risks, such as hearing loss, facial nerve dysfunction, postoperative headache, and cerebrospinal fluid leakage, a "look and re-examine" approach is adopted for most patients. Radiotherapy is a useful alternative and has been shown to have a similar response to growth restriction.[4]

Intracanalicular injury of the internal auditory nerve represents VS in most cases. In the presence of facial paralysis, this could possibly represent facial neuroma, although they involve the labyrinthine/tympanic or mastoid segment of the facial nerve. The rare but possible differential diagnosis of the lesions needs to be considered when dealing with the reviewed region carefully before concluding the lesion as VS exclusively. With the improvement of imaging modalities, attention should be paid to detailed MRI. Discussing the case with the neuroradiology team should be a routine protocol that could help avoid misdiagnoses of the disease.[5]

The radiological characteristics of this tumor are not specific in conventional MRI, and advanced imaging techniques, such as diffusion-weighted MRI (DWI), diffusion tensor imaging, MRI perfusion, and MRI spectroscopy, have been shown to be useful for differentiating primary lymphomas of the central nervous system from other neoplasms. According to Arcuri et al.[6] MR spectroscopy played an important role in the diagnosis of primary cerebellopontine angle lymphoma and in the differentiation of this from acoustic schwannoma or meningioma.

Lymphoma can occasionally mimic VS, presenting diagnostic challenges due to clinical and radiographic similarities. The correct identification of these masses is crucial for proper management. Masses in the cerebellopontine and intracanalicular angle may be misdiagnosed as VSs, with a small percentage revealing themselves as other diagnoses, including lymphoma. The clinical presentation of unilateral progressive sensorineural hearing loss, tinnitus, and vestibular dysfunction, together with a contrast-enhancing mass in the internal auditory canal on MRI, is suggestive of VS, but may be lymphoma, especially in patients with HIV. Its most common symptoms include hearing loss and tinnitus, with only half of patients experiencing vertigo attacks, which can be similar to the clinical presentation of VS-mimicking lymphomas.[7]

Epidemiology and etiology

Schwannomas account for 8-10% of all intracranial tumors and 75% of tumors cerebellopontine angle. The overall incidence is 3-5 cases per 100,000 person-years, and in the age group over 70 years, the incidence rises to 20 cases per 100,000 person-years. This estimate has increased in recent decades due to the dissemination of more accurate imaging tests, such as contrast-enhanced MRI. However, it is believed that the prevalence is higher than what has already been verified, since many cases are asymptomatic and have slow growth.[1]

VS is unilateral 95% of the time and usually has sporadic onset. However, the relationship with the highest incidence of these tumors in patients with neurofibromatosis is known. The bilateral presentation is pathognomonic of neurofibromatosis type 2. This relationship should also be suspected in patients with unilateral tumors and younger than 40 years of age, since most sporadic cases are diagnosed between the sixth and seventh decade of life.[1,2] These tumors originate due to the loss of a tumor suppressor gene on the long arm of chromosome 22. In cases of neurofibromatosis type 2, this condition can be inherited or passed on to the next generations in an autosomal dominant manner.[2]

Clinical presentation

Clinical manifestations vary considerably depending on the location and size of the tumor, as well as the compression of other nearby cranial nerves. The classic symptomatic triad is ipsilateral hearing loss (>90%), asymmetric tinnitus (55%), and dizziness or imbalance (up to 61%).[1]

Initially, due to the involvement of the vestibular portion of the VIII nerve, imbalance occurs, and in less than 20% of cases, true vertigo may occur. However, as the tumor grows, vestibular function is centrally compensated, which reduces the intensity and perception of this symptom. A clinical sign that may be present is nystagmus or electronystagmography altered by caloric stimulation.

Sensorineural hearing loss and high-pitched tinnitus occur when there is compression of the auditory nerve in the internal auditory canal, which is usually the main complaint that leads to seeking medical attention. The more lateralized the tumor is in the internal auditory canal, the earlier the hearing loss. Hearing loss tends to be unilateral, progressive, and insidious. Up to 70% of patients have hearing loss with predominance in high frequencies (4,000 to 5,000 Hertz) and decreased word discrimination. Although less frequent, about 10% may report sudden hearing loss. Therefore, VS should always be considered as a differential diagnosis in patients with sudden deafness.[2]

Larger tumors can compress the facial nerve and trigeminal nerve, causing hypoesthesia with trigeminal distribution, secondary trigeminal neuralgia, paresthesia, facial weakness and spasms, and even changes in taste. In addition, compression of the brainstem and lower cranial nerves may occur, resulting in symptoms depending on the function of the affected structure. Compression of the cerebellum can lead to dysbasia, dysmetria, or cerebellar ataxia. Schwannomas larger than 4 cm can lead to secondary hydrocephalus due to obstruction that hinders cerebrospinal fluid resorption.

Symptoms arising from facial nerve, trigeminal motor, or lower cranial nerve dysfunction are possible, but are uncommon even in large tumors. Therefore, when present, they should be considered differential diagnoses.[1]

Diagnosis

Currently, the gold standard in tumor investigation is gadolinium contrast MRI, due to its high sensitivity (98%) and excellent specificity, allowing the detection of even very small tumors. However, in cases of unavailability of this exam or contraindication, it is possible to resort to contrast-enhanced computed tomography.

Tumors that have a rounded or oval shape in the center of the internal auditory canal are suggestive of VS, as well as narrowing of the base of the internal auditory canal. These tumors may present isointensity or hyperintensity on T1-weighted sequences and hyperintensity on T2-weighted sequences, in addition to exhibiting heterogeneity in contrast uptake.[1-3] It is important to note that schwannomas larger than 3 cm in diameter can also resemble cystic areas, despite being predominantly solid.

It is essential to perform the differential diagnosis with other tumors that affect the cerebellopontine angle, such as meningiomas, epidermoid tumors, arachnoid cysts, and metastases.

Evaluation

In addition to imaging tests, audiometric evaluation is recommended, including pure-tone audiogram and vocal discrimination tests. For patients with small tumors (1.5 cm or less), nystagmography and vestibular evoked myogenic potential, which evaluate the upper and lower division of the vestibular nerve, respectively, is advisable. These tests help in understanding the location of the tumor in relation to its depth and proximity to the cochlear nerve. In addition, auditory brainstem response testing can provide information about the prognosis of hearing preservation.

Evolution

VS usually exhibits indolent behavior and may remain stable for long periods or have extremely gradual growth. It is considered slow growing when it reaches up to 2 mm per year, while it is classified as fast when it exceeds 1 cm per year. In addition, it is important to note that some tumors can regress, involuting up to about 1 mm per year.

Various series demonstrate different growth rates, with averages ranging from 1 mm/year, and in some cases, up to 40% of tumors remained unchanged

for up to 80 months.[3] Other studies indicate even more frequent and lasting stability, with 52% of cases without growth in a 9-year period, and 76% of patients under observation not requiring treatment during this period.[3]

In the last 15 years, it has been reported that only 22-48% of tumors showed growth over 2.[6-7.3] years of follow-up.[1]

It is crucial to emphasize that the worsening of audiovestibular symptoms is not a reliable indicator of tumor growth.[1]

Treatment

To determine the treatment approach, it is essential to consider several factors, including the size of the tumor, the patient's neurological condition, their age, other coexisting medical conditions, and the patient's own preference. This may lead to a choice between expectant management or the implementation of active treatment.

Conservative management involves observation of symptoms, hearing, and tumor growth with periodic imaging tests. If there is evidence of progression of the VS (growth greater than 2 mm), intervention is indicated. During the first 2 years after diagnosis, MRI is recommended every 6 months. If the tumor remains stable, annual examinations are sufficient in subsequent years, with repeated programs for 5, 7, 9, and 14 years after diagnosis.[2] The audiological evaluation must be carried out annually. For continuous surveillance, contrast-enhanced MRI or high-contrast T2-weighted, thin-slice MRI cisternography can be used.

Therapeutic options include radiosurgery, microsurgery or chemotherapy, and can be applied alone or in combination.

For patients with small tumors (<15 mm) and functional hearing, expectant management is indicated. Medium-sized tumors (15-20 mm) are preferentially treated, especially in the young, but may be seen if multiple comorbidities are present or if the patient is elderly. On the other hand, for large tumors (>25 mm), the recommendation is always to treat, regardless of age.[2]

Observational management can prevent morbidities and even treatment-related mortality. However, the increase in tumor size over time can make the operation more challenging. In addition, it is important to highlight that hearing loss is a natural evolution of the disease that can occur regardless of the treatment chosen and does not present a greater risk in cases where expectant management is adopted.[1]

In patients with neurofibromatosis type 2, the approach should be evaluated on an individual basis, as they often have a more challenging prognosis in the management of tumors, with higher rates of recurrences and nerve deficits. Early treatment is generally considered the best option, and in some cases, chemotherapy, such as the use of bevacizumab, may offer a satisfactory response.[2]

Radiosurgery aims to slow tumor growth, but it does not lead to a cure or removal of dysfunctional tissue. It is important to note that in the first 3 years after radiosurgery, there may be a transient increase in the volume of the schwannoma, but in more than 50% of cases, the tumor involutes after treatment. Follow-up after radiosurgery should include audiological evaluations and MRI every 2 years for the first 10 years and then every 5 years indefinitely. Studies have demonstrated efficacy in tumor control in more than 90% of VS cases over a 10-year period. However, failure may occur that requires further intervention, such as in cases of symptoms caused by the mass effect, persistent growth after 3 years, or accelerated growth. The main indication for radiosurgery is the treatment of tumors less than 2.5 cm in diameter, but it can be considered in tumors smaller than 3 cm. It is important to note that there are associated risks, such as permanent facial nerve weakness, trigeminal neuropathy, secondary neoplasia, among others.

Microsurgery can be performed on tumors of all sizes, but it is the conduct of choice for bulky tumors with a mass effect. There are several possible access routes, including the retrosigmoid, translabyrinthine and middle fossa. Advances in surgical techniques, the use of surgical microscopes, and intraoperative neurophysiological monitoring have led to better rates of facial nerve preservation and postoperative hearing.

The retrosigmoid approach is capable of preserving hearing, while the translabyrinthine generally does not, becoming more indicated when the patient does not have functional hearing. Midfossa access is recommended for small, lateralized tumors with hearing-preserving potential, but may present a higher risk of facial nerve damage, especially if the surgeon is less experienced.[2]

After the operation, patients may experience continuous fatigue and imbalance, which tend to disappear within 3 months. Follow-up with MRI should be performed for the first 12 months, followed by periodic surveillance according to the specific indications of each case. Risks associated with the operation include decreased facial nerve function and hearing, which are related to the size of the tumor and the complexity of the surgical procedure. Other possible complications include postoperative cerebrospinal fluid fistula (9-13%), aseptic meningitis (2-4%), bacterial meningitis (1%) among others.[1]

The objective of microsurgery, regardless of the route chosen, is the maximum excision of the tumor with preservation of neurological functions. In cases of strong adherence of the tumor to the 7th, cranial nerve or to the brainstem, it may be necessary to perform almost total or subtotal resection of the tumor and to monitor the tumor remnant with serial imaging tests.

Some patients may require rehabilitation intervention such as those who have had facial nerve palsy, bilateral hearing loss, dizziness, or chronic imbalance. In cases of hearing loss, it is also possible

to consider operations for bone conduction implants or the use of non-surgical hearing devices, such as hearing aids, to improve this function.

Tumor-related facial nerve topography

Predicting the course of the facial nerve by means of preoperative imaging tests is of great importance for the establishment of a more appropriate surgical plan and the reduction of complications, in addition to presuming the estimation of postoperative results in relation to the functional preservation of the facial nerve.

Several factors are associated with the risk of facial paralysis after surgical resection, including previous radiation therapy, tumor location, direction of growth, and size. These factors can lead to displacement of the facial nerve and adhesion or stretching of its nerve fibers over the mass.[4]

The rate of anatomical injury of the facial nerve due to the operation is generally less than 5% in different series. However, the long-term preservation rate of facial nerve functional integrity (assessed as grade I of the House-Brackmann scale) is about 60% in some studies involving large SVs.[5]

The position of the facial nerve in relation to the tumor can vary and there are more frequent standard conditions: anterior or ventral, anterosuperior, anteroinferior and dorsal or posterior. The 7th cranial nerve, in its anatomical position, usually occupies the anterosuperior quadrant of the internal auditory canal, and its course varies according to the size of the tumor, site of origin, and degree of adhesion.[6,7]

Studies carried out to assess the position and path of the facial nerve confirm these variations and highlight what is most frequently seen in practice. For example, a series of 100 patients undergoing VS microsurgery found the anterosuperior position to be predominant, especially in small tumors (<15 mm), while larger tumors showed an increase in the incidence of anterior and anteroinferior patterns, with no case reported in the posterior position. This study also suggested that anterosuperior and anteroinferior patterns are associated with better postoperative outcomes in preserving facial nerve function. In addition, tumors larger than 3 cm in diameter showed greater adhesion of the facial nerve to the tumor capsule, leading to more neural deficits after the procedure.[6]

In contrast to these results, another series of patients, consisting of 356 cases, reported a predominance of the anterior position in small schwannomas.[8] Similar to what was found in a larger series, involving 1,006 cases, Sampath et al.[9] described the predominance of facial nerve presentation anteriorly in all tumor sizes, as the second highest frequency in the anterosuperior position.

Although advances in the field of imaging have been made, accurate identification of the preoperative facial nerve is still challenging. Currently, the most reliable method is the use of the surgical microscope associated with repeated intraoperative nerve stimulation. Other options that can aid in surgical planning include cisternography and tractography.[10]

Diffusion tractography is a modern MRI technique that can provide three-dimensional images of white matter fibers, but it still has some limitations, such as the difficulty in distinguishing the facial nerve from the vestibular nerve and the possibility of focal deletion due to the effect of tumor mass. Therefore, validation by intraoperative monitoring is essential.[5]

A retrospective study with 19 cases evaluated the accuracy of tractography in comparison with the result obtained by describing the intraoperative course of the 7th nerve. In 84% of the cases, the tractography was successful, and in 94% of them, it corresponded to the intraoperative description of the nerve position. However, it is important to exercise caution when using this technology, since it presented significant discrepancies in relation to the actual position (3D tumor model) compared to that of tractography, reaching up to 3.7 mm (+/- 4.[2] mm) difference.[11]

Furthermore, in another study, Borkar et al.[12,] found an accuracy of 90.9% in a sample with 22 patients. Similarly, other authors[9] reported an accuracy of 71% when analyzing 21 patients, while Borkar et al.[12] described an accuracy of 89% in 16 treated patients.

CONCLUSION

Although VS is characterized by symptoms such as hearing loss and tinnitus, other conditions, including lymphoma, may present with similar clinical symptoms and radiological findings. Accurate identification of these masses is essential, as treatment and prognosis can vary significantly. Awareness of the possibility of lymphoma in patients with typical VS symptoms, especially in immunosuppressive settings such as HIV, is important for differential diagnosis. The importance of the review as a way to address the risk factors and diagnosis of VS, was observed due to the chance of medical treating in specific cases that require surgical treatment.

Authors' contributions

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Advancements in Alzheimer's disease: early diagnosis, biomarkers, and future perspectives

Avanços na doença de Alzheimer: diagnóstico precoce, biomarcadores e perspectivas futuras

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ABSTRACT

Introduction: Recent advancements in biomarker research and diagnostic frameworks, such as the ATN classification system, have redefined the approach to early diagnosis and treatment. However, challenges remain in differentiating biological from clinical AD and in ensuring equitable access to emerging therapeutic interventions.

Objective: Explore the latest advancements in AD diagnosis and management, focusing on biomarkers, neuroimaging techniques, molecular insights, and future therapeutic approaches.

Method: An integrative review was conducted using PubMed, Scopus, and Embase databases. Inclusion criteria encompassed systematic reviews, meta-analyses, and clinical guidelines discussing AD pathophysiology, diagnostics, and therapeutic developments. Studies with inadequate methodology or duplicate data were excluded.

Result: Advances in molecular diagnostics, including amyloid and tau biomarkers, have significantly enhanced early detection of AD. The ATN framework categorizes the disease's progression, integrating neurodegenerative and inflammatory markers. Novel imaging techniques, such as TRODAT and PET-FDG, offer improved disease monitoring. Immunological therapies, particularly monoclonal antibodies like aducanumab and lecanemab, have shown promise in slowing disease progression, but accessibility and cost remain major barriers.

Conclusion: While substantial progress has been made in AD diagnosis and treatment, critical challenges persist regarding early detection, therapeutic efficacy, and healthcare accessibility. Future research should focus on integrating precision medicine approaches, developing cost-effective interventions, and expanding preventive strategies.

KEYWORDS: Alzheimer's disease. Early diagnosis. Biomarkers. Future perspectives.

RESUMO

Introdução: Avanços recentes na pesquisa de biomarcadores e estruturas diagnósticas, como o sistema de classificação ATN, redefiniram a abordagem do diagnóstico e tratamento precoces. No entanto, permanecem desafios na diferenciação da DA biológica da clínica e na garantia de acesso equitativo a intervenções terapêuticas emergentes.

Objetivo: Explorar os mais recentes avanços no diagnóstico e tratamento da DA, com foco em biomarcadores, técnicas de neuroimagem, insights moleculares e futuras abordagens terapêuticas.

Método: Foi realizada uma revisão integrativa nas bases de dados PubMed, Scopus e Embase. Os critérios de inclusão abrangeram revisões sistemáticas, metanálises e diretrizes clínicas discutindo fisiopatologia, diagnóstico e desenvolvimentos terapêuticos da DA. Foram excluídos estudos com metodologia inadequada ou dados duplicados.

Resultado: Os avanços no diagnóstico molecular, incluindo biomarcadores amilóides e tau, melhoraram significativamente a detecção precoce da DA. A estrutura ATN categoriza a progressão da doença, integrando marcadores neurodegenerativos e inflamatórios. Novas técnicas de imagem, como TRODAT e PET-FDG, oferecem melhor monitoramento da doença. As terapias imunológicas, particularmente anticorpos monoclonais como aducanumabe e lecanemab, mostraram-se promissoras em retardar a progressão da doença, mas a acessibilidade e o custo continuam sendo as principais barreiras.

Conclusão: Embora tenham sido feitos progressos substanciais no diagnóstico e tratamento da DA, persistem desafios críticos em relação à detecção precoce, eficácia terapêutica e acesso aos cuidados de saúde. Pesquisas futuras devem se concentrar na integração de abordagens de medicina de precisão, no desenvolvimento de intervenções econômicas e na expansão de estratégias preventivas.

PALAVRAS-CHAVE: Doença de Alzheimer. Diagnóstico precoce. Biomarcadores. Perspectivas futuras.

Central Message

Recent advancements in Alzheimer's disease (AD) research, particularly in biomarker discovery, diagnostic frameworks like the ATN classification system, and novel therapeutic approaches, have significantly enhanced early diagnosis and monitoring of the disease. However, challenges persist in differentiating biological from clinical AD, and in ensuring equitable access to emerging treatments, such as monoclonal antibodies. Despite substantial progress, critical issues remain regarding early detection, treatment efficacy, and healthcare accessibility.

Perspective

Future research in AD should focus on integrating precision medicine approaches, which tailor treatments to individual patients based on genetic, environmental, and lifestyle factors. Additionally, there is a need to develop cost-effective therapies and expand preventive strategies to ensure broader access to emerging treatments. Addressing these challenges will be essential for improving both the clinical outcomes for patients and the accessibility of care across diverse populations.

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INTRODUCTION

Alzheimer's disease (AD) represents the most prevalent form of dementia, accounting for approximately 60–80% of diagnosed cases worldwide. It is a progressive neurodegenerative disorder characterized by the gradual deterioration of cognitive, behavioral, and motor functions, with profound implications for the individual's functionality and the caregivers' quality of life.[1] It is no longer synonymous with dementia. Biological AD constitutes risk factor for cognitive decline, which may take years to manifest clinically or may never do so. The biological diagnosis of it is of great importance due to advancements in the detection of pathological hallmarks prior to the onset of clinical symptoms, utilizing biomarkers identified in cerebrospinal fluid and neuroimaging modalities. A critical challenge lies in distinguishing between biological and clinical AD and effectively communicating the implications of this paradigm shift to healthcare professionals and the general population. This is essential to mitigate stigma and prevent premature decisions regarding patients' careers or lifestyles. Additionally, the paucity of evidence regarding the efficacy of interventions in the very early stages of the disease further complicates this discussion.[2,3]

This review aims to explore recent diagnostic advancements and to examine future perspectives in the treatment of this condition. The objective is to provide a comprehensive overview to enhance understanding and support the ethical management of this complex disease.

METHOD

This integrative literature review was conducted searching the PubMed, Scopus, and Embase databases. Articles addressing the pathophysiology of AD, diagnostic advancements, biomarkers, current treatments, and future perspectives were included. Inclusion criteria encompassed: studies exploring pathophysiological, diagnostic, or therapeutic aspects, systematic reviews, meta-analyses, and clinical guidelines. Additionally, articles discussing the ethical considerations of early and biological diagnosis of AD were included. Duplicate studies and those with inadequate methodology were excluded. The objective was to compile updated and relevant information, providing a comprehensive overview of the current state of knowledge on AD. So, 26 papers were included in this review.

DISCUSSION

Current understanding of Alzheimer's disease

The pathophysiology of AD is predominantly explained by the amyloid-tau hypothesis, which suggests that the extracellular accumulation of beta-amyloid plaques and the intracellular formation of hyperphosphorylated tau neurofibrillary tangles act as primary triggers for neurodegeneration. These pathological processes lead to a cascade of events, including synaptic dysfunction, neuroglial inflammation, neuronal death, and progressive brain atrophy. The hippocampus and temporoparietal regions are among the earliest affected areas, correlating with the memory deficits and spatial disorientation that characterize the initial stages of the disease.[4,5]

Beyond the amyloid-tau axis, several other factors contribute significantly to the complex pathophysiology of AD. Oxidative stress and mitochondrial dysfunction play a critical role in amplifying cellular damage, while neuroinflammation driven by hyperactive microglia exacerbates neuronal injury and synaptic loss. Additionally, alterations in brain glucose metabolism, often described as "cerebral insulin resistance," further impair neuronal function and energy homeostasis.[4,5]

Genetic predisposition also exerts a profound influence on the risk of developing AD, with the presence of the apolipoprotein E4 (ApoE4) allele being the strongest genetic risk factor identified to date. ApoE4 is associated with increased beta-amyloid deposition and impaired clearance, as well as heightened vulnerability to neuroinflammatory processes and metabolic disturbances.[6]

Together, these interconnected mechanisms underscore the multifactorial nature of AD, reflecting a complex interplay between genetic, molecular, and environmental factors that drive the progression of this debilitating neurodegenerative disorder.

Perspectives on Alzheimer's disease

The understanding and management of AD have evolved significantly, particularly with recent advances in dementia prevention, intervention, and care, as outlined in the 2024 Report of the Lancet Standing Commission. This report highlights the multifaceted nature of AD, encompassing its prevention, early diagnosis, and comprehensive care. Central to these efforts are frameworks such as the ATN classification system, which has refined the understanding of AD pathophysiology and diagnostic criteria, and innovations like the use of transcriptomics for a molecular-level understanding of the disease.[7]

The ATN system and reactive astrocytes

The ATN (Amyloid, Tau, Neurodegeneration) framework categorizes biomarkers for AD into 3 core pathological domains. In this system, "A" represents amyloid beta disease; "T" refers to tau-related abnormalities; and "N" indicates neurodegeneration. This classification has become a cornerstone for stratifying patients in clinical and research settings, enabling targeted interventions.[8]

Reactive astrocytes play a crucial intermediary role within the ATN system. Following the deposition of beta-amyloid plaques, astrocytes are activated and become reactive. These cells, intimately associated with cerebral vasculature, mediate the transition from amyloid pathology (A) to tau hyperphosphorylation (T). Their vascular interactions suggest a role in modulating the blood-brain barrier and influencing

downstream tau-related changes. Understanding the timing and mechanisms of astrocyte reactivity may provide a window for therapeutic intervention before extensive tau pathology develops.[9]

Neurodegeneration and biomarkers

Neurodegeneration, as measured by neuronal atrophy and functional decline, is a critical element of the ATN system. It is closely associated with a reduction in glucose metabolism, which can be visualized using PET-FDG scans. Neuroimaging plays a pivotal role in identifying and monitoring the progression of neurodegenerative changes. Markers such as TRODAT, which measure dopamine transporter activity, are emerging as tools to understand dopaminergic dysfunction and its relation to cognitive decline in AD. While primarily linked to Parkinsonian disorders, TRODAT findings in AD may reveal overlapping pathophysiological mechanisms involving synaptic and neurotransmitter integrity.[9]

Advances in diagnosis and molecular insights

Diagnostic paradigms for AD continue to evolve with consensus guidelines such as the AA2024 and IWG2021 criteria. These frameworks emphasize the integration of biomarkers into clinical diagnosis, moving beyond symptomatic assessment to molecular characterization. Advances in transcriptomic technologies are shedding light on the gene expression profiles associated with Alzheimer's pathology. These insights not only enhance the understanding of disease mechanisms but also pave the way for personalized medicine approaches.[10,11]

The field of AD research and management has undergone substantial evolution, as highlighted by the 2024 report from the Lancet Standing Commission. A critical focus of contemporary research lies in dementia prevention, intervention, and care, with an emphasis on integrating novel diagnostic tools and therapeutic strategies that target early stages of the disease.[7]

One cornerstone of this advancement is the ATN (Amyloid, Tau, Neurodegeneration) framework, which provides a structured approach for classifying AD pathology using biomarkers. The ATN system delineates the pathophysiological progression of AD, where amyloid-beta deposition (A) precedes tau hyperphosphorylation (T) and neurodegeneration (N). Emerging evidence suggests that reactive astrocytes play a pivotal role at the A-to-T transition, mediating vascular and inflammatory responses that contribute to the downstream tau pathology. This astrocytic activity represents a potential therapeutic target, bridging the molecular gap between amyloid and tau cascades.[4-8]

The concept of neurodegeneration in AD is closely associated with neuronal atrophy and loss of function, which can be quantitatively assessed through glucose metabolism via imaging modalities such as PET-FDG. The introduction of TRODAT, a dopamine transporter imaging marker, expands the scope of molecular diagnostics, enabling more refined assessments of neural integrity beyond traditional amyloid and tau markers. These advancements align with international guidelines such as the IWG 2021 and AA 2024 frameworks, which advocate for biomarker-driven definitions of AD to enhance diagnostic precision.[9,11,12]

Transcriptomic analyses are another frontier in AD research, offering insights into gene expression profiles associated with disease progression. These data not only elucidate the molecular underpinnings of AD but also aid in identifying novel therapeutic targets. Meanwhile, the identification of 14 modifiable risk factors underscores the importance of prevention. Lifestyle interventions — ranging from physical activity and dietary modifications to cognitive training — are increasingly recognized as integral components of dementia prevention strategies.[5,6,8]

Immunology and biomarker-based therapies: a paradigm shift

The advent of immunology-based therapies, including monoclonal antibodies such as aducanumab and lecanemab, has marked a paradigm shift in AD management. These therapies aim to mitigate amyloid burden and slow cognitive decline, exemplifying the potential of precision medicine. However, significant barriers persist. High costs and limited accessibility to these advanced treatments disproportionately affect low- and middle-income countries, exacerbating global health inequities.[13]

Biomarker-driven approaches not only facilitate earlier diagnoses but also enable tailored interventions that align with an individual's specific pathological profile. Despite these advances, their widespread implementation is hindered by infrastructural and economic limitations, underscoring the need for scalable solutions to democratize access to these technologies.

Differential diagnosis Alzheimer's disease

AD is the most common form of dementia in the elderly, with its prevalence increasing markedly with age. Aging is the most significant risk factor for the development of AD, although family history and genetic predisposition also contribute. However, autosomal dominant familial forms, typically characterized by an early onset (before the age of 65), account for less than 5% of all cases. Among genetic factors, the presence of the apolipoprotein E4 (ApoE4) allele is highly associated with both sporadic and familial cases of AD.[1,3-6]

From a pathological perspective, AD is characterized macroscopically by cortical atrophy, particularly in associative neocortical areas and mesial temporal regions, such as the hippocampus. Microscopically, intracellular neurofibrillary tangles composed of tau protein and extracellular deposits of beta-amyloid peptide in neuritic plaques are hallmark findings. Neuropathological examination remains the gold standard for the diagnosis of AD, based on the distribution and quantity of these lesions.[4-6]

Clinically, the earliest and most prominent feature is episodic memory impairment. This typically

manifests as difficulty recalling recent events, repetitive questioning, and misplacing personal items. In some cases, AD may initially present as amnestic mild cognitive impairment, where functional independence is preserved, and dementia is not yet established. As the disease progresses, involvement of the frontal, temporal, and parietal associative cortices leads to the emergence of additional cognitive and behavioral symptoms. Although the amnestic presentation is the most common, non-amnestic forms are also recognized, particularly in early-onset AD cases.[8,9]

The most accurate biological markers currently include structural and functional neuroimaging and cerebrospinal fluid biomarkers. Structural imaging, particularly brain MRI, typically reveals atrophy of mesial temporal structures and dilation of the temporal horns of the lateral ventricles. Cerebrospinal fluid analysis shows increased tau and hyperphosphorylated tau proteins with decreased beta-amyloid levels. Functional neuroimaging, such as positron emission tomography (PET) with fluorodeoxyglucose, demonstrates characteristic posterior temporoparietal hypometabolism.[8-11]

Vascular dementia

Vascular disease is now recognized as one of the most identifiable and modifiable risk factors for dementia, alongside aging. The most widely accepted criteria for diagnosing vascular dementia are those established by the National Institute of Neurological Disorders and Stroke – *Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN). These criteria require the presence of dementia associated with cerebrovascular disease, which is defined by neurological examination findings or imaging evidence, along with a clear relationship between the two. Such a relationship may include the onset of dementia within 3 months of a recognized stroke, an abrupt cognitive decline, or a stepwise progression of cognitive deficits.[13]

Several features strengthen the diagnosis, such as early gait disturbances (e.g., petit-pas or apraxic gait), reports of imbalance, pseudobulbar palsy, early urinary urgency, and personality or mood changes. Conversely, the presence of early and progressive amnestic deficits, the absence of vascular lesions on imaging, or the lack of focal neurological signs makes the diagnosis less likely. The pathophysiology of cognitive impairment in vascular dementia — now frequently referred to as vascular cognitive impairment — involves small vessel disease leading to cerebral white matter changes (leukoaraiosis), strategic or extensive small infarcts, and diffuse subcortical lesions. These changes disrupt neural networks, resulting in variable symptoms depending on the vascular territory affected and the extent of the damage.[14]

The progression rate of vascular dementia is variable and may be slower than that observed in AD. However, the mortality rate tends to be higher in vascular dementia. With advancements in stroke management and better control of vascular risk factors, this trend may change in the coming years. Continued research is needed to clarify the interplay between vascular pathology and neurodegenerative processes and to optimize therapeutic strategies for this complex condition.[13,14]

Frontotemporal dementia

Frontotemporal lobar degeneration (FTLD) encompasses a heterogeneous group of neuropathological diagnoses and distinct clinical syndromes. It is the second most common cause of degenerative dementia in individuals under 65 years of age, with AD being the first. FTLD presents with different predominant syndromes: when behavioral changes dominate, it is classified as the behavioral variant of FTLD (bvFTLD). Conversely, when language impairments predominate, the condition is termed primary progressive aphasias, which include semantic dementia and non-fluent/agrammatic progressive aphasia.[15]

In the behavioral variant, symptoms stem from damage to the prefrontal lobe, including reduced empathy, inappropriate affect, irritability, and loss of self-awareness. Apathy, linked to anterior cingulate gyrus involvement, is a hallmark feature. Other symptoms include altered food preferences, hypersexuality, and utilization behavior, which are associated with orbitofrontal damage. Patients with right temporal lobe involvement may exhibit antisocial behaviors, hyperreligiosity, and compulsive tendencies. Cognitive assessments typically reveal executive dysfunction, with relatively preserved memory and visuospatial abilities. Parkinsonism is observed in approximately 20% of cases.[16-18]

Semantic dementia manifests as a fluent language disorder characterized by the progressive loss of word knowledge and comprehension, often accompanied by semantic paraphasias. Pathologically, it is associated with asymmetric anterior temporal atrophy, predominantly linked to TDP-43 proteinopathy. Non-fluent/agrammatic progressive aphasia, on the other hand, features agrammatism, speech apraxia, and phonemic paraphasias, with a marked reduction in word production and articulation difficulties.[16-18]

Diagnosing FTLD relies on neuroimaging techniques such as brain MRI and FDG-PET, which can reveal patterns of atrophy and hypometabolism characteristic of the condition. In pre-senile cases, cerebrospinal fluid analysis is also recommended to support the diagnosis. Ongoing research into biomarkers and genetic contributions continues to refine diagnostic accuracy and inform treatment strategies for this complex group of dementias.[16-18]

Dementia with Lewy bodies (DLB)

DLB is recognized as the second most common cause of neurodegenerative dementia, surpassed only by AD. It is characterized by progressive dementia accompanied by parkinsonism — typically symmetrical with minimal tremor —recurrent visual hallucinations, and cognitive fluctuations.[15]

Cognitive fluctuation is among the most prevalent symptoms, affecting up to 90% of patients. It manifests as variations in attention, consciousness, and daytime somnolence. Visual hallucinations often emerge in the early stages of DLB, contrasting with AD, where they typically appear later. Parkinsonism in DLB demonstrates a limited response to levodopa, aiding in the differential diagnosis. Cognitive assessments in DLB often reveal impairments in attention, visuospatial skills, and constructional praxis, while episodic memory is relatively preserved in the early stages. Functional neuroimaging techniques, such as SPECT and PET, can assist in diagnosis by showing reduced perfusion or metabolism in the posterior parietal and occipital regions.[19,20]

Assessment tests

The diagnostic workup for dementia requires a comprehensive approach involving cognitive testing, laboratory analyses, and imaging studies to exclude reversible causes and confirm the underlying pathology.[15]

Cognitive testing plays a pivotal role in assessing the extent and nature of cognitive impairment. Standardized tools such as the Montreal Cognitive Assessment, the Mini-Mental State Examination, verbal fluency tests, and the clock-drawing test are employed to evaluate memory, executive function, language skills, and visuospatial abilities. These assessments provide critical insights into the pattern of cognitive deficits, which may guide differential diagnosis.[21-23]

Laboratory investigations are essential to exclude metabolic or infectious causes of cognitive decline. Routine tests include measurements of vitamin B12 levels and thyroid-stimulating hormone to identify deficiencies or thyroid dysfunction, renal function tests to detect underlying nephropathy, assessment of electrolytes for imbalances, and inflammatory markers to rule out systemic or central nervous system infections.[21-23]

Neuroimaging is a cornerstone in the evaluation of dementia, offering structural and functional insights. Magnetic resonance imaging is utilized to detect hippocampal atrophy, a hallmark of AD and other neurodegenerative conditions. Advanced functional imaging techniques, such as amyloid positron emission tomography (PET) and fluorodeoxyglucose PET (FDG-PET), are valuable for detecting amyloid plaques and evaluating cerebral metabolic activity, respectively. These modalities help distinguish between different types of dementia and provide prognostic information.[23]

This integrative diagnostic approach is critical for accurately characterizing the type and stage of dementia, guiding treatment decisions, and facilitating individualized patient care.

Emerging perspectives

In recent years, monoclonal antibodies such as aducanumab and lecanemab have demonstrated promising efficacy in slowing cognitive decline by reducing cerebral beta-amyloid burden. These developments represent a paradigm shift in the treatment landscape of neurodegenerative diseases, particularly AD. Additionally, ongoing research into tau protein modulators offers a complementary avenue for addressing neurofibrillary pathology. Non-pharmacological approaches, including deep brain stimulation, have also gained significant attention, with preliminary findings suggesting potential benefits in modulating neural networks and improving cognitive function.[12]

Other notable advancements include the early identification of individuals at high risk for dementia through genetic testing and biomarker profiling. Advances in precision medicine have enabled the stratification of patients based on their genetic and biochemical profiles, paving the way for targeted interventions. Furthermore, lifestyle-based interventions aimed at enhancing cognitive reserve have emerged as a vital component of preventive strategies. These interventions encompass tailored physical activity programs, cognitive training, and nutritional optimization, underscoring the importance of a holistic approach to mitigating the impact of neurodegenerative diseases.[3,8,15]

Collectively, these advancements reflect a multi-faceted approach to dementia research and care, integrating pharmacological innovations, technological breakthroughs, and preventive strategies to address the complex challenges posed by these disorders.

Modifiable risk factors and prevention strategies

The identification of 14 modifiable risk factors for dementia, including hypertension, diabetes, obesity, physical inactivity, and social isolation, has shifted the focus toward prevention. Targeted interventions addressing these factors could potentially delay or prevent up to 40% of dementia cases worldwide. Lifestyle modifications, such as cognitive engagement, physical activity, and vascular health optimization, are now integral to comprehensive dementia prevention strategies.[4,6]

The integration of innovative diagnostic tools, such as TRODAT imaging and transcriptomics, alongside the ATN framework, represents a paradigm shift in the approach to AD. These advances are complemented by a growing emphasis on prevention through the modification of risk factors. As highlighted by the 2024 Lancet Report, the future of AD management will likely depend on a combination of early detection, molecularly targeted therapies, and broad-based preventive measures. Together, these strategies aim to reduce the burden of AD and improve the quality of life for affected individuals and their families.[7]

Future directions and challenges

The future of AD research must prioritize several key areas to drive meaningful progress. First, therapeutic interventions should aim to intervene earlier in the amyloid-tau cascade, particularly at the A-to-T

transition, to alter the disease's trajectory before irreversible damage occurs. Second, preventive strategies targeting at-risk populations are crucial, with an emphasis on lifestyle modifications such as physical activity and dietary interventions to reduce the incidence and delay disease progression.[3]

Furthermore, the integration of Artificial Intelligence into AD research has the potential to revolutionize diagnostic capabilities, enabling more accurate risk prediction, early detection, and real-time monitoring of disease progression, thereby improving patient outcomes.

The field stands at a critical crossroads, with significant advances in biomarkers, immunological therapies, and transcriptomic research paving the way for personalized treatment approaches. However, overcoming economic and infrastructural barriers to access remains essential, particularly in low- and middle-income countries, to ensure that these innovations benefit all patients. As the scientific community continues to decode the complexities of AD, a balanced focus on early intervention, prevention, and scalable solutions will be paramount in translating these breakthroughs into tangible global health improvements.[3]

Limitations

As a narrative review, the ability to quantitatively assess the effectiveness of the new therapies and interventions discussed is constrained. The qualitative analysis limits the objectivity of the findings, making it difficult to draw direct comparisons across different approaches and to establish firm conclusions regarding their relative efficacy.

The article did not include grey literature, such as unpublished theses, dissertations, and reports, which may result in a somewhat limited perspective on the current state of AD. The omission of such sources could potentially overlook important studies and findings not published in peer-reviewed journals.

The review did not incorporate comprehensive longitudinal data regarding the progression of the disease, which would provide a more robust understanding of how novel therapies influence the natural course of AD over time. Long-term follow-up studies are essential for evaluating the sustained impact of interventions.

The analysis of biomarkers and emerging immunological therapies is constrained by the availability and accessibility of these advanced diagnostic tools. This limitation may not reflect the real-world application in settings with limited resources, where these technologies might not be readily available.

The lack of data from diverse and representative populations may hinder the generalizability of the findings. Given the disparities in healthcare access and technological availability, especially in low- and middle-income countries, the conclusions may not be applicable across different demographic groups or geographic settings.

CONCLUSION

AD remains one of the most formidable challenges in modern medicine due to its high prevalence and profound impact on quality of life. Advances in understanding its pathophysiology and the development of novel biomarkers have been instrumental in enabling early diagnosis and refining therapeutic strategies. However, significant hurdles persist, including the high costs of new treatments, inequitable access, and limitations in therapeutic efficacy. The ultimate goal in the field is to develop effective treatments that not only address symptoms but also prevent the onset of dementia. Nevertheless, diagnosing AD based solely on clinical and biological constructs without a comprehensive understanding of when the symptoms will manifest is both premature and problematic. It is recommended that amyloid-positive individuals or those with biomarker evidence of AD but who remain cognitively normal should not be labeled as having AD. Instead, these individuals should be considered at risk for AD, with the expansion of presymptomatic AD as a more accurate diagnostic construct. This approach emphasizes biomarkers as indicators of proximity to symptom onset, rather than definitive diagnoses. Future research directions should focus on two critical areas: longitudinal observational studies that simultaneously evaluate lifestyle risk factors and biomarkers to determine their independent contributions to cognitive impairment and dementia over extended follow-up periods. Interventional clinical trials testing the efficacy of therapies targeting Alzheimer's pathology and other risk reduction strategies, aiming to decrease the incidence of cognitive impairment while carefully assessing the therapeutic risk-benefit profiles, are needed. Moreover, early diagnosis based on biomarkers could improve prognostic accuracy and inform variations in mortality risk. However, the translation of these advancements into clinical practice requires robust investments in both basic and translational research, alongside effective public health policies to ensure accessibility and equity. These efforts are essential for transforming the landscape of AD care in the coming decades.

Author´s contribution

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Surgical treatment of Parkinson's disease - up to date 2024

Tratamento cirúrgico da doença de Parkinson, up to date 2024

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ABSTRACT

Introduction: As a slow and progressive neurological disorder, Parkinson's dementia is caused by the loss of dopamine-secreting cells in the gray matter of the basal ganglia. Its clinical characteristic is mainly through bradykinesia (slowness of voluntary movements) with rigidity and/or tremor. One of the ways to relieve motor and cognitive symptoms is neural stimulation, with contraindications for cases where the disease presents itself in an atypical way, very advanced age, significant comorbidity, advanced cognitive deficit and/or major psychic disorder.

Objective: To address the use of the deep brain stimulation technique by evoked interference, its results and its impact on the quality of life of patients.

Method: Articles were selected from the PubMed and ScienceDirect databases, from 2021-2023 in English and Portuguese.

Result: 250 articles were analyzed, of which 13 were selected to compose the present review.

Conclusion: Surgical treatment using evoked interference for Parkinson's disease proved to be effective taking into account the individuality of each patient, showing positive results for improving quality of life.

KEYWORDS: Parkinson's disease. Deep brain stimulation. Evoked interference. Surgical treatment. Quality of life. Motor symptoms. Cognitive impairment. Neurosurgical therapy.

RESUMO

Introdução: Sendo transtorno neurológico lento e progressivo, a demência de Parkinson tem como uma das causas a perda de células secretoras de dopamina na substância cinzenta dos núcleos da base. Sua característica clínica se apresenta principalmente através da bradicinesia (lentidão dos movimentos voluntários) com rigidez e/ou tremor. Uma das formas de alívio de sintomas motores e cognitivos é a estimulação neural, sendo suas contraindicações para casos onde a doença se mostra de maneira atípica, idade muito avançada, comorbidade significativa, déficit cognitivo avançado e/ou transtorno psíquico maior.

Objetivo: Abordar o uso da técnica de estimulação cerebral profunda por interferência evocada, seus resultados e seu impacto na qualidade de vida dos doentes.

Método: Foram selecionados artigos nas bases de dados PubMed e ScienceDirect, no período de 2021-2023 em inglês e português. Resultado: 250 artigos foram analisados, dos quais 13 selecionados para compor a presente revisão.

Conclusão: O tratamento cirúrgico com uso de interferência evocada para a doença de Parkinson mostrou-se eficaz levando-se em consideração a individualidade de cada paciente mostrando resultados positivos para a melhora na qualidade de vida.

PALAVRAS-CHAVE: Doença de Parkinson. Estimulação cerebral profunda. Interferência evocada.Tratamento cirúrgico. Qualidade de vida. Sintomas motores. Déficit cognitivo. Terapia neurocirúrgica.

Central Message

The main message of the article is that the evoked interference has the potential to significantly improve the quality of life of patients with Parkinson's disease, but the successful application of the technique requires a personalized and careful approach. In addition, while the results are encouraging, more studies are needed to refine and fully understand the impact of evoked interference, especially with regard to cognitive and long-term effects.

Perspective

The article addresses a modern therapeutic approach to the treatment of Parkinson's disease through deep brain stimulation with evoked interference. The central perspective is that, although the surgical technique is promising for alleviating its motor and cognitive symptoms, its efficacy depends on careful selection of patients and stimulation parameters. This underscores the importance of individualized assessment, taking into account factors such as cognitive impairment and the presence of comorbidities.

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INTRODUCTION

The loss of dopamine-secreting cells in the gray matter of the basal ganglia is one of the causes involved in the development of Parkinson's dementia (PD), which is a slow and progressive neurological disorder.[1] The main characteristic of this disease presents as bradykinesia (slowness of voluntary movements) with rigidity and/or tremor; in addition, it may contain other findings during clinical inspection such as fixed and expressionless face with reduced blinking frequency, polyphonic voice, drooling, impairment of rapid alternating movements, micrographia, reduced arm sway, hunched and flexed posture when walking, shuffling gait, difficulty starting or stopping gait, block turning (multiple small steps to turn around) and retropulsion.[2,3]

Treatment for PD can be provided by pharmacological and non-pharmacological routes. It is worth noting that there is no neuroprotective therapy established for or approved for neuroprotection modification of the disease in an effective way, but there are drugs with potential in clinical studies.[4,5]

One of the ways used to treat the motor and cognitive symptoms of PD is deep neural stimulation (DBS), which is indicated for patients with a 4-year variation in uncontrolled motor functions.[6] In addition, deep neural stimulation is indicated primarily for patients with disability resulting from severe tremor or levodopa-induced motor complications. The procedure is quite beneficial for many patients. Contraindications to surgery include atypical PD, advanced cognitive impairment, major psychiatric disorder, significant medical comorbidity, and advanced age (relative contraindication).[7]

The objective of this article was, through a narrative review, to address the use of the technique of deep brain stimulation by evoked interference, its results and impact on the quality of life of PD patients.

METHOD

This is a narrative review in the PubMed and ScienceDirect databases using the DeCS/MeSH descriptors "Surgery" and "Treatment" and "Parkinson's disease". The period was from 2021 to 2023. A total of 390 articles were found, according to the inclusion criteria, language in English, Portuguese and Spanish, free text in full, defined theme in neurosurgery and relevant aspects on the guiding issue, such as techniques for the surgical treatment of Parkinson's, the importance and need for the use of these corrective techniques, as well as some of their advantages. In the end, 250 articles were analyzed, of which 13 were selected to compose the present review.

Figure presents the detailed flowchart of the study selection process. Those included varied in their research objects, ranging from the analysis of hospital data to the investigation of the feasibility of advanced DBS techniques and their effects on different aspects of PD. Tables 1 and 2 provide a detailed overview of the studies included in this review. Table 1 characterizes those based on authorship, journal, and object of study. Table 2 describes the objectives and main results found in the analyzed articles.

FIGURE — Flowchart on the choices of articles

DISCUSSION

According to studies, surgical treatment for PD has been shown to be effective in patients. However, as in any type of surgical procedure, the individuality of each patient must be taken into account. Careful selection of parameters, such as precise target location and stimulation intensity, can influence the level of post-procedure cognitive impairment. For Galivache et al.[5] PD is an important potential risk factor for postoperative complications in elective patients with elective anterior cervical discectomy and fusion. Therefore, it is concluded that the importance of the relationship between surgical characteristics and outcomes is essential when there is a patient with PD who wishes to undergo surgical intervention.[7-9]

The intervention can be done through the technique of deep brain stimulation by evoked interference (eiDBS). For Sanabria et al.[6] The use of eiDBS has been shown to be effective in controlling anomalous oscillations in the globus pallidus, providing relief of motor symptoms in PD patients. According to Chu et al.[7,] the use of eiDBS in both the globus pallidus and the subthalamic nucleus (STN) induces different topographic reconstructions in the brain, either in the motor area or in the control of emotions and cognitive functions. Therefore, an individualized study of each patient and their symptoms is necessary for decision-making in the choice of treatment and subsequent improvement of the patient's quality of life.[10-12]

The feasibility of using DBS in patients with marked motor oscillation brings a new approach by highlighting the possibility of algorithms in neural interface with the use of biomarkers. However, it is worth highlighting the need to promote more studies to analyze its application due to the low number of research participants. The use of bilateral STN-DBS has been shown to have a potential neurorestorative of dopaminergic systems, contributing to the improvement of the clinical picture caused by PD. Sensorimotor SNR shows an increase in coupling force after electrode implantation, especially in the somatomotor area, which is in line with clinical improvement after surgical procedure in DBS. In

TABLE 1 — Characterization of studies according to authorship, year of publication, journal, language, and object of study[4-16]

Authorship	Periodic	Object of study
Chu et al.[7]	Neuroimage	In 34 patients with DBS in STN (n=17) or GPi (n=17) and in 16 healthy controls, resting fMRI was collected in the ON and OFF states of stimulation. From there, functional connectivity networks were set up and local efficiency and clustering coefficient were calculated by graph theory. Finally, changes in these metrics in motor areas were correlated with improvement in the UPDRS-III score.
Galivanche et al.[5]	North American Spine Society Journal	NIS data from 2008-2018 on anterior cervical spine procedures were used and later refined to ACDF using ICD-9 and ICD-10 criteria.
Mulders et al.[4]	Clinical Neurology and Neurosurgery	A total of 49 patients were chosen for the study, in which 20 patients were included in a previous study.
Sanabria et al.[6]	Brain Stimulation	A 55-year-old male diagnosed with PD at 6 years.
Santos et al.[12]	NeuroImage: Clinical	Data from the resident population (n=1184) were analyzed, including 629 women with a mean age of 59.6 years and standard deviation of +/- 7.29 years, collected in a longitudinal study with more than 15 years of observation every 5 years. In addition, 13 women with a mean age of 64.4 years and standard deviation of +/- 6.41 years were used to use PD patients recruited by a special clinic for movement disorders, who had previously participated in another study.
Taira et al.[13]	Clinical Neurology and	About 51 patients with PD who were referred to the department from April 2014 to March 2016 were evaluated
Zhou et al.[14]	NeuroImage: Clinical	101 individuals diagnosed with idiopathic PD from the Department of Neurology of the 2nd Affiliated Hospital of Zhejinang Medical University.
Swann et al.[8]	Journal of Neural Engineering	Feasibility of using adaptive DBS using a fully implanted neural prosthesis.
Fauser et al.[9]	Neurobiology of Disease	How Cellular Plasticity in Dopaminergic Systems is Affected by STN-DBS
Koverola et al.[16]	Journal of Experimental Social	To assess the effects caused by deep stimulation systems on universal human domains, memory, emotional intelligence, and general intelligence.
Butenko et al.[11]	NeuroImage: Clinical	To correlate patient-specific pathway activation profiles and clinical motor improvement.
Sure et al.[10]	NeuroImage: Clinical	to investigate whether the stunning effect related to DBS also modulated the RSNs. 51 people in total were studied (the RSN of 27 patients with PD and 24 RSN of healthy patients was analyzed).
Chen et al.[15]	Brain Hemorrhages	To analyze the responses obtained with SNT-DBS from 28 patients with PD (with advanced stage), preoperatively, one month and one year after surgery.

TABLE 2 — Description of the objectives and results of the articles used

Authorship	Goals	Findings
Chu et al.[7]	to investigate how DBS in two distinct targets STN and GPi reorganizes the topology of brain functional networks in patients with Parkinson's disease, evaluating changes in the efficiency of information processing and transmission in the states with DBS on (ON) and off (OFF) in relation to healthy controls.	The results demonstrate that the topographic changes induced by STN-DBS and GPi-DBS in motor regions not associated with cognition and emotion are inverse and may differ in permanence.
Galivanche et al.[5]	To perform a comparison with in-hospital outcomes after elective anterior cervical discectomy and fusion (ACDF) in cases of patients with and without PD.	With data showing 3948 cases of elective ACDF in patients with PD, which represents 0.31% of the total elective surgeries. It was found that patients with PD had higher chances of mild adverse effects during hospital stay compared to severe events and mortality when compared to patients without PD.
Mulders et al.[4]	To analyze the association between surgical features and cognitive decline after deep brain stimulation in the subthalamic nucleus in PD	The study shows that the passage of the electrode can subtly contribute to changes in executive functions, however only a few patients showed a relevant cognitive decline and the impact is low. In addition, the use of MER and a longer length of the STN are not associated with cognitive decline 1 year after surgery, nor was an improvement in motor function observed, concluding that DBS is a safe technique.
Sanabria et al.[6]	To test the feasibility of controlling pathological neural oscillations in the subthalamic nucleus in real time in patients with PD.	The study demonstrated positive results regarding the control of neural oscillations through eiDBS, however, it has limitations that should be taken into account.
Santos et al.[12]	Investigate how PD may affect the motor areas that overlap in the subthalamic nucleus and globus pallidus.	A similar structural covariance pattern was observed in the GPi and the mSTN analyzing several anatomical features of the brain, however the study states that there are still some limitations.
Taira et al.[13]	To perform an assessment of pharyngeal and upper esophageal sphincter motility in patients with PD using the high-resolution pharyngeal manometry technique.	The results of the high-resolution pharyngeal manometry (HRPM) technique showed quantitative changes in swallowing pressure in patients with PD depending on the stage of the disease. This demonstrates the effectiveness of HRPM, in addition to being a safe and simple method.
Zhou et al.[14]	To investigate the association between locus ceruleus degeneration and functional dissociation present in PD.	The relationship between locus ceruleus degeneration and cognitive impairment in PD patients has been confirmed.
Swann et al.[8]	Here they seek to show how varied stimulation in real time can be beneficial or not in 2 patients.	Feasibility of using adaptive DBS for PD patients who have motor oscillations and have marked dyskinesia alternating with severe bradykinesia. In addition, it demonstrates not only the possibility of an algorithm development approach in a neural interface, using sensing for biomarker exploration, but also the use of control algorithms completely inserted in the deep stimulation device.
Fauser et al.[9]	How Cellular Plasticity in Dopaminergic Systems is Affected by STN-DBS	Possibility of using bilateral STN-DBS as a neurorestorative in nigrostriatal and mesolimbic dopaminergic systems.
Koverola et al.[16]	To assess the effects caused by deep stimulation systems on universal human domains, memory, emotional intelligence, and general intelligence.	More studies are needed to reach a concrete conclusion.
Butenk et al.[11]	To correlate patient-specific pathway activation profiles and clinical motor improvement.	Studies suggest that the use of DBS, as a form of induction in specific pathways, improves the response to the relief of motor symptoms. The optimization emphasized moderate activation in specific pathways of the brain while avoiding stimulation in another area.
Sure et al.[10]	to investigate whether the DBS-related stunning effect also modulated the RSNs.	DBS significantly reduced symptoms in patients in the OFF-medication state, but did not improve in patients on ON-medication. Sensorimotor SNR showed an increase in coupling force after electrode implantation, especially in the somatomotor area, in line with clinical improvement after DBS surgery.
Chen et al.[15]	To analyze the responses obtained with SNT-DBS from 28 patients with PD (with advanced stage), preoperatively, one month and one year after surgery.	He suggested that in patients with advanced PD with distinct axial symptoms, memory decline, and visual hallucination, they need a more careful and complete analysis for the implant.

addition, optimization of treatment by its means should focus on moderate activation in specific pathways of the brain, avoiding stimulation in other areas to improve the response in relieving the motor symptoms of PD. On the other hand, patients with advanced PD and distinct axial symptoms, memory decline, and visual hallucination require more careful and complete analysis before performing DBS implantation. It is also worth noting the possibility of interference in the universal humanistic domains caused by deep neural stimulation. However, the study did not show a full conclusion on how DBS can affect these domains, requiring further studies for a better understanding.[13-16]

CONCLUSION

The use of DBS in the surgical treatment of patients with PD is capable of improving symptoms and quality of life, especially if done in an individualized and thorough manner with the patient in order to maximize results. Surgery contributes to the improvement of symptoms depending on the nucleus stimulated and can return to

the patient an improvement in the performance of daily activities, restoring quality of life. The use of DBS should always be accompanied by a more careful and complex analysis of the patient. In specific pathways, it reveals positive results for the relief of motor symptoms in PD, and it is worth noting that its application in patients in a state of OFF-medication has shown significant results for an even greater reduction of motor symptoms. DBS is a possible and beneficial option in those with motor oscillation and intense dyskinesia, and bilateral DBS in the STN should be highlighted as an option as neurorestorer in the dopaminergic systems. It can be observed that deep neural stimulation is still a promising and positive treatment in cases of PD on OFF-medication, and it is necessary to observe the particularities of each case, location and intensity of stimulation, especially where the disease presents greater progress and specific symptoms. More studies need to be carried out to better understand how DBS affects human universal domains and the applicability of algorithms with the use of biomarkers in more cases of PD.

Authors' contributions

Alan de Paula Ferreira Barros: Validation, Writing – review & editing
Giovana Nascimento Antocheviez: Data curation, Writing – original draft
Ricardo Silva dos Santos: Project administration
Samir Ale Bark: Formal analysis, Methodology
Marianna Cassini Soares da Costa: Validation, Writing – review & editing

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Association between autism and gastrointestinal changes: a systematic review

Associação entre autismo e alterações gastrointestinais: uma revisão sistemática

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ABSTRACT

Introduction: The association between autism and gastrointestinal disorders has been increasingly investigated, with studies suggesting that children with autism may have a higher susceptibility to intestinal problems, although the nature of this relationship remains unclear.

Objective: To systematically review the most recent scientific evidence on the relationship between autism spectrum disorder and gastrointestinal disorders, aiming to clarify its implications for diagnosis and treatment.

Method: A systematic review was conducted in the BVS, Medline, and PubMed databases using the descriptors "gut microbiota" and "autism". Fifty-nine articles that met the inclusion criteria were selected.

Result: The analysis showed variations in results but indicated a possible higher predisposition of children with autism to gastrointestinal disorders, although the exact relationship remains undefined. The connection between autism and gastrointestinal problems is complex and still uncertain, highlighting the need for further research to improve understanding and treatment.

Conclusion: There is evidence of a relationship between autism and gastrointestinal disorders, but more studies are needed to clarify this association and improve the clinical management of autism spectrum disorder.

KEYWORDS: Autism. Gastrointestinal disorders. Neurology. Gastroenterology.

Central Message

The association between autism and gastrointestinal disorders has been increasingly investigated, with studies suggesting that children with autism may be more susceptible to intestinal problems, although the nature of this relationship is still unclear. Thus, there is a need to promote scientific evidence on the relationship between autism spectrum disorder and gastrointestinal disorders.

Perspective

Evidence of microbial dysbiosis in autism spectrum disorder has progressed over the past decade, and immunological and gastrointestinal dysfunction may be linked to dysbiosis. However, there is some evidence that altering the microbiota may improve behaviors, i.e., achieving a balance between beneficial commensals and potentially pathogenic microbes in the gut, with the aim of directly contributing to the quality of life of children with the disorder.

RESUMO

Introdução: A associação entre autismo e distúrbios gastrointestinais tem sido cada vez mais investigada, com estudos sugerindo que crianças com autismo podem ter maior suscetibilidade a problemas intestinais, embora a natureza dessa relação ainda não esteja clara.

Objetivo: Revisar sistematicamente as evidências científicas mais recentes sobre a relação entre transtorno do espectro autista e distúrbios gastrointestinais, visando esclarecer suas implicações para o diagnóstico e tratamento.

Método: Foi realizada uma revisão sistemática nas bases de dados BVS, Medline e PubMed, utilizando os descritores "gut microbiota" e "autism". Cinquenta e nove artigos que atenderam aos critérios de inclusão foram selecionados.

Resultado: A análise mostrou variações nos resultados, mas indicou uma possível maior predisposição de crianças com autismo a distúrbios gastrointestinais, embora a relação exata permaneça indefinida. A conexão entre autismo e problemas gastrointestinais é complexa e ainda incerta, destacando a necessidade de mais pesquisas para melhorar a compreensão e o tratamento.

Conclusão: Há evidências de uma relação entre autismo e distúrbios gastrointestinais, mas mais estudos são necessários para esclarecer essa associação e melhorar o manejo clínico do transtorno do espectro autista.

PALAVRAS-CHAVE: Autismo. Distúrbios gastrointestinais. Neurologia. Gastroenterologia.

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INTRODUCTION

Autism spectrum disorders (ASD) are part of a series of heterogeneous neurodevelopmental disorders characterized by deficits in communication, social interaction, and cognition. ASD does not have a single defined etiology, and contemporary theories suggest a range of genetic and environmental contributions.[1] A diverse range of genetic and environmental elements has been identified as contributors to the development of ASD. These factors range from genetic predispositions to environmental influences, including nutritional deficiencies, exposure to viral agents, failures in the embryonic closure process of the neural tube, dysfunctions in the immune systems, and allergic manifestations. The convergence of these complex factors highlights the multifaceted and interdisciplinary nature of the etiology of ASD, emphasizing the importance of an integrative approach in understanding the underlying mechanisms of this neuropsychiatric disorder. Given that genetic mechanisms are responsible for approximately 10-20% of ASD cases, the etiological heterogeneity becomes even broader, promoting the study of a possible relationship between ASD and other physiological changes, such as gastrointestinal disorders, which are interconnected with an alteration of the gut-brain axis leading to intestinal dysbiosis precursors of disorders such as increased intestinal permeability, general changes in the microbiota, and the occurrence of intestinal infection and inflammation.[2,3]

The evidence of microbial dysbiosis in ASD has progressed in the last decade, just as immune and gastrointestinal dysfunction may be linked to dysbiosis. However, there is some evidence that the alteration of the microbiota in ASD may improve behaviors, i.[e.,] achieving a balance between beneficial commensals and potentially pathogenic microbes in the intestine, aiming to contribute directly to the quality of life of children with ASD.[4,5] Despite the its complexity in understanding the exact pathogenesis, in recent research has highlighted the relevance of the interaction between the intestinal microbiota and the brain in patients with autism and other neuropsychiatric conditions. Individuals with ASD often present notable gastrointestinal dysfunctions, such as changes in bowel habits and chronic abdominal pain, which correlate with their neurological manifestations. The microbiota, a microbial community composed of trillions of microorganisms, plays a significant role in various conditions, including those of the nervous system.[6]

The relationship between the intestinal microbiota and the central nervous system, known as the "gut-brain axis," emerges as a crucial element in neuropsychiatric disorders, including autism. This review focuses on analyzing dysbiosis in ASD, especially exploring the possible connection between gastrointestinal disorders, inflammation, and neurobehavioral symptoms in autistic children.

The objective of this review was to conduct a comprehensive systematic review of current studies to investigate the association between autism and gastrointestinal changes, aiming to provide an in-depth understanding of contemporary knowledge on this subject. So, it proposed to identify and analyze recent studies examining the prevalence of gastrointestinal changes in individuals with autism, considering different age groups and social backgrounds; to evaluate the quality of the studies with a focus on methodology, sampling, diagnostic criteria, and statistical approaches to validate the results; to synthesize the available evidence to determine a significant association between autism and gastrointestinal changes, exploring potential risk factors and possible underlying mechanisms.

METHOD

The articles were selected through a search in the following databases: Virtual Health Library (BVS), specifically targeting works from the International Literature in Health Sciences (Medline) and PubMed. The descriptors used were "gut microbiota" and "autism," conducting an advanced search by combining the descriptors with the boolean operator AND. Inclusion criteria encompassed publications available freely in full, in English and Portuguese, published within the last 5 years, specifically addressing autism spectrum disorder and intestinal microbiota. Incomplete or repetitive articles, preliminary clinical trials in animals, or those encompassing other psychopathologies unrelated to ASD were excluded. The initial search on Pubmed yielded 444 articles, with 31 selected for analysis. On the Medline platform, 96 articles were found, with 28 selected, totaling 59 articles.

RESULT

To view the description of the summarized articles of this study use the QR Code bellow or click on the link below the QR Code to open the supplementary file.[1-59]

Supplementary file

DISCUSSION

ASD is characterized by a behavioral syndrome that affects numerous stages of normal mental development, and recently, progress in diagnosis has been reported, with an average of 1 case per 88 children. Children with ASD exhibit speech and language disorders, learning difficulties, intellectual impairment, and motor impairments. In addition to neurological impairment, current research explores the relationship between ASD and other physiological changes, such as gastrointestinal disorders, which are clearly linked to altered intestinal microbiota composition.[7]

The genetic basis of ASD is extremely complex, as more than 100 genes and genomic regions directly or indirectly related to the etiology of ASD have

been discovered. This includes genes involved in the development of the central nervous system and approximately 400 genes that may confer susceptibility to autism.[8,9] It is understood that the effects on quality of life, in a subtle manner, vary from person to person. Thus, verbal and non-verbal intelligence quotients (IQs) and repetitive and restricted behaviors can range from stereotyped motor behaviors at a low level to a high level.[10]

In the last decade, there has been a growing fascination with studying the role of intestinal microbiota as a co-factor in ASD development, as numerous studies have addressed a possible bidirectional communication between the brain and the intestine, referred to as the gut-brain axis.[11]

The communication axis between the brain and the intestine is regulated at various levels, with the nervous and endocrine systems serving as the main regulators, including the central role of the HPA axis (hypothalamus-pituitary-adrenal axis), as well as the immune pathway. Regarding the immune regulation of the HPA axis, it is predominantly mediated by changes in cytokine organization. On the other hand, nervous regulation primarily occurs through the transmission of impulses in the autonomic nervous system, including the vagus nerve, afferent and efferent fibers, and the enteric nervous system, often referred to as the "intestinal brain." This system not only directly regulates the muscles, mucosa, and blood vessels of the digestive tract but also influences their activity. Additionally, resident microorganisms in the intestine, such as certain species of bacteria and fungi, also play a role in communication with the immune system and the enteric nervous system through the synthesis and distribution of various neurotransmitters.[12,13]

Hypothalamic hormones, such as corticoliberin and vasopressin, initiate a hormonal cascade along the HPA axis, stimulating the anterior pituitary gland to produce and secrete the adrenocorticotropic hormone. These hormones, in turn, stimulate the adrenal gland to secrete glucocorticoids, mainly cortisol, which plays a fundamental role in this complex interaction between the brain and the gastrointestinal system. The brain-gut axis, establishing a strong connection between the brain, intestines, and intestinal microbiota, represents a bidirectional communication pathway, where the interaction between the brain and the gastrointestinal system is mainly mediated by the nervous system, with an emphasis on the vagus nerve.[14,15]

In individuals with ASD, food restriction, difficult eating behaviors, and gastrointestinal disorders are easily observed. This is because children with autism are predominantly selective eaters, showing aversion to colors, textures, smells, or specific characteristics of numerous foods. This directly correlates with the composition of the intestinal microbiota, nutritional deficiencies, and diet quality. Additionally, it is common for children with autism to exhibit abnormalities in gastrointestinal physiology, including increased intestinal permeability, general changes in microbiota, intestinal infections, as well as immune dysfunction and gastrointestinal inflammation.[16,17]

Moreover, among the ASD-affected population, the relationship between gastrointestinal symptoms and behavioral abnormalities can vary according to the patient's age, implying significant clinical implications in addressing gastrointestinal disorders in children with ASD. Chronic constipation emerges as one of the most prominent gastrointestinal symptoms, often coexisting with core symptoms of ASD.[18,19]

These changes in intestinal microbiota during early life development may influence neurodevelopment, contributing to adverse effects on mental health throughout life. Therefore, further investigation is needed to understand changes in the abundance and diversity of bacteria accompanying ASD, especially when associated with constipation, which may reveal potential effects of the interaction between ASD and gastrointestinal symptoms resulting from dysbiosis of the intestinal microbiota and fecal metabolites.[20,21]

Despite the specific volume of studies published on dysbiosis in the intestinal microbiota of individuals with ASD, there is still no anticipated consensus regarding the precise composition of the intestinal microbiome specific to these individuals, and some studies present conflicting results. This variation in results can be attributed, in part, to the lack of uniformity in factors such as age, diet, medication, geographic location, presence of comorbidities, and severity of neurobehavioral and gastrointestinal symptoms among the patients involved in the studies. For example, the fecal microbiota of younger individuals has a lower proportion of Bacteroidetes compared to older individuals, and the microbiome profile may vary depending on the specific section of the gastrointestinal tract from which the sample was collected. Therefore, for a precise comparison and evaluation of results related to intestinal microbiota in ASD, studies with more homogeneous patient groups are necessary.[22]

Despite numerous studies highlighting the potential of antibiotics in alleviating gastrointestinal and behavioral symptoms in ASD, controversies persist regarding this type of treatment. Initially, bacteria not only eradicate harmful atmospheric bacteria but also exhibit characteristics of beneficial bacteria in ASD patients, potentially increasing susceptibility to gastrointestinal issues in children with ASD. Therefore, antibiotic therapy may not be an ideal intervention to restore the balance of the intestinal microbiota.[23-25]

Recently, studies on dietary interventions for children with ASD have gained popularity. Among these, the Mediterranean diet stands out as relatively easy to introduce to children. On the other hand, the adherence to a ketogenic diet, while offering benefits, is challenging for this target population.[26]

Furthermore, probiotics are live microorganisms that, when consumed in specific formulations, confer health benefits to the host. On the other hand, prebiotics consist of non-digestible fibers, such as oligosaccharides, which stimulate the growth and optimize the functionality of probiotics in the gastrointestinal tract, acting as specific substrates. Initial evidence suggests that supplementation of probiotics and prebiotics may have a promising

preventive effect on neurological and mental health conditions, including Alzheimer's disease, Parkinson's disease, depression, and notably, ASD.[27,28]

However, due to the wide variation in treatments applied, the duration of therapeutic protocols, and the tools used to assess outcomes, the data obtained do not allow for a definitive decision regarding the benefits of probiotics and other interventions in relation to ASD symptoms. Given the inherent diversity in ASD, it would be advantageous to select therapeutic approaches based on the specific characteristics of each individual with ASD and their microbiota, with the ultimate goal of personalizing therapy.[29-31]

Another significant study contributing to treatment evolution was providing additional evidence on modulating the gastrointestinal tract microbiota through fecal microbiota transplantation, probiotics, and dietary therapy. Literature from the last half-decade considers that probiotics prevent intestinal diseases by regulating and controlling the blood-brain barrier. Fecal microbiota transplantation, on the other hand, is an interventional approach where fecal microorganisms from healthy individuals are delivered to patients with a depleted microbiota, but the safety and effectiveness of this approach are still under speculation.[32-38]

In summary, therapeutic approaches for ASD centered on the intestinal microbiome include dietary therapy, antibiotic therapy, probiotic and prebiotic intervention, as well as microbial transfer therapy. Additionally, it is relevant to explore diverse perspectives among researchers regarding the relationship between the intestinal microbiome and autism, questioning whether variations in the observed microbiota in the intestines of autistic children result from their restricted dietary preferences associated with autism diagnosis characteristics or are correlated with underlying reasons for behavioral symptoms.[39,40]

CONCLUSION

Based on the aforementioned, it is concluded that current studies on the link between autism and gastrointestinal changes emphasize the complexity of this ever-evolving relationship. Although there are indications that children with autism may be more susceptible to gastrointestinal disorders, the true nature of this connection remains elusive. This uncertainty underscores the ongoing need for more in-depth and comprehensive research efforts, not only to identify the association between these conditions but also to investigate how it may impact the diagnosis and treatment of autism. Additionally, this review highlights the importance of a multidisciplinary approach in the assessment and care of individuals with autism, integrating attention to gastrointestinal needs as an essential component of treatment. A more solid understanding of this relationship can provide valuable guidance to healthcare professionals and parents, with the potential to enhance the quality of life and overall well-being of individuals with autism. This represents a significant step toward more comprehensive and personalized care for this community.

Author´s contribution

Guilherme Nobre Nogueira: Formal analysis, Methodology
Nicole Custódio Porto Silva: Validation, Writing – review & editing
Hugo Lorran Souza Costa: Data curation, Writing – original draft
Poliana Zago Perondi: Conceptualization, Investigação
Rafaela Fernandes Gonçalves: Formal analysis, Methodology
Gustavo Henrique Tomasi: Project administration

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Association between Vitamin D deficiency and Parkinson's disease: systematic review of the evidence on therapeutic potential and causal relationship

Associação entre deficiência de Vitamina D e doença de Parkinson: revisão sistemática das evidências sobre potencial terapêutico e relação causal

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ABSTRACT

Introduction: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies. Genetic mutations and oxidative stress contribute to its progression. Vitamin D may play a neuroprotective role in PD, but its therapeutic potential remains uncertain.

Objective: This review aims to assess the relationship between vitamin D deficiency and the development, prognosis, and therapeutic potential in PD.

Method: A systematic review was conducted using the descriptors "vitamin D" and "Parkinson's disease" in the PubMed and MedLine databases. Fourteen studies published in the last 5 years, focusing on human clinical and epidemiological data, were selected.

Result: The studies suggest that low levels of 25(OH)D increase the risk of PD, although there is no association with symptom severity. Vitamin D influences neurotrophic factors, aiding in the maintenance of dopaminergic neurons and improving tissue microcirculation. The neuroprotective role of vitamin D includes the regulation of neurotrophic factors and the protection of neurons against oxidative stress.

Conclusion: Although there is no consensus on the therapeutic role of vitamin D in PD, evidence suggests its influence on the development of the disease. Investigating vitamin D levels at the onset of PD is crucial, especially to prevent bone density loss and fall-related complications.

KEYWORDS: Vitamin D deficiency. Parkinson's disease. Therapy.

RESUMO

Introdução: A doença de Parkinson (DP) é doença neurodegenerativa caracterizada pela perda de neurônios dopaminérgicos na substância negra e pela formação de corpos de Lewy. Mutações genéticas e estresse oxidativo contribuem para sua progressão. A vitamina D pode desempenhar um papel neuroprotetor na DP, mas seu potencial terapêutico permanece incerto.

Objetivo: Esta revisão tem como objetivo avaliar a relação entre a deficiência de vitamina D e o desenvolvimento, prognóstico e potencial terapêutico na DP.

Método: Foi realizada uma revisão sistemática utilizando os descritores "vitamina D" e "doença de Parkinson" nas bases de dados PubMed e MedLine. Quatorze estudos publicados nos últimos 5 anos, com foco em dados clínicos e epidemiológicos humanos, foram selecionados.

Resultado: Os estudos sugerem que baixos níveis de 25(OH)D aumentam o risco de DP, embora não haja associação com a gravidade dos sintomas. A vitamina D influencia os fatores neurotróficos, auxiliando na manutenção dos neurônios dopaminérgicos e melhorando a microcirculação tecidual. O papel neuroprotetor da vitamina D inclui a regulação de fatores neurotróficos e a proteção dos neurônios contra o estresse oxidativo.

Conclusão: Embora não haja consenso sobre o papel terapêutico da vitamina D na DP, evidências sugerem sua influência no desenvolvimento da doença. Investigar os níveis de vitamina D no início da DP é crucial, especialmente para prevenir a perda de densidade óssea e complicações relacionadas a quedas.

PALAVRAS-CHAVE: Deficiência de vitamina D. Doença de Parkinson. Terapia.

Central Message

Parkinson's disease (PD) involves loss of dopaminergic neurons, and vitamin D deficiency may increase its risk. Although there is no consensus on its therapeutic role, evidence suggests that low vitamin D levels influence the development of PD.

Perspective

Vitamin D deficiency appears to be linked to an increased risk of Parkinson's disease, but its therapeutic potential is still uncertain. Further studies are needed to clarify its real influence in the treatment of PD.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by the reduction of dopaminergic neurons present in the substantia nigra of the midbrain and the deposition of alpha-synuclein proteins in the cytoplasm of neurons, thus forming Lewy bodies. Although it is an idiopathic condition, it is noted that mutations in genes responsible for the production of alpha-synuclein, LRRK2, parkin, and PINK1 proteins trigger mitochondrial changes which, consequently, cause oxidative stress in neuronal tissue, with a subsequent increase in reactive oxygen species, thus contributing to the progression of PD.[1,2]

The corresponding neuromotor dysfunction is multifactorial, being mainly associated with genetic predisposition, advanced age, male gender, use of medications, exposure to chemicals, and smoking. Clinical manifestations arise with the progression of the disease, when the majority of dopaminergic neurons have been damaged, being manifested by motor symptoms — tremors, bradykinesia, postural instability, and rigidity — and non-motor symptoms — cognitive decline, dysfunction of the autonomic nervous system, psychiatric disorders, and sleep disorders.[3]

PD management is multidisciplinary and must consider the clinical stage of the pathology, symptoms, and the individuality of the patient. The available and commonly prescribed pharmacological options are levodopa, MAO-B inhibitors, glutamate pathway antagonists, catechol-O-methyltransferase (COMT) inhibitors, and non-ergot dopaminergic agonists.[3]

The numerous advances related to knowledge of the pathophysiology and therapy of PD are notable. Some studies show a possible association between vitamin D deficiency and this disease. The corresponding vitamin can be obtained through diet or sun exposure, requiring a series of reactions to activate. The first step takes place in the liver and involves the hydroxylation of cholecalciferol (D3) or ergocalciferol (D2), resulting in the formation of 25-hydroxyvitamin D. Subsequently, the same process takes place in the kidneys, but to generate 1,25-hydroxyvitamin D, the active form of vitamin D, which is capable of binding to the specific receptor and carrying out its actions. It is worth noting that this vitamin also has receptors in various brain regions, thus exerting a neuroprotective function by inhibiting the activation of microglia and, in this way, protecting dopaminergic neurons and increasing the neurotrophic factor expression. Despite the existence of some divergences regarding this association, there is some evidence of the influence of hypovitaminosis on the individual's prognosis, mainly in the maintenance of postural instability and impairment of motor condition.[4]

Therefore, to clarify the role played by vitamin D in development, prognosis, and therapeutic potential, this paper summarize the main scientific data that allow critical evaluation and understanding of this possible association.

METHOD

The method used in this systematic review has as its starting point the formulation of the following research question: What is the relationship between vitamin D and Parkinson's disease? To address this question, the descriptors "vitamin D" and "Parkinson's disease" were used during the bibliographic search. The search was conducted in the VHL (MedLine) and PubMed databases, following specific selection criteria. Were included studies with full text available in Portuguese and English, published in the last 5 years, and which focused on clinical, epidemiological, and observational approaches, all aimed at exploring the relationship between vitamin D and Parkinson's disease in humans. In vitro and animal studies and those that expanded the scope to other neurodegenerative diseases were excluded, to maintain the focus on the proposed theme. Data extraction covered essential information, such as author, year of publication, title, objectives, methods, sample size, results, and conclusions. The methodological quality of the selected studies was carefully evaluated. In the initial search, 84 results were identified in PubMed and 142 in MedLine. Of these, 9 and 5, respectively, were selected for analysis, following the previously established inclusion criteria, totaling 14 articles for the present review (Table).[5-17]

RESULT

Metadata and content analysis of articles (n = 14) (Tabla)

DISCUSSION

Vitamin D plays a significant role in synaptic plasticity by modulating the neurotrophic factors responsible for the process of neuronal proliferation and differentiation, such as glial cell-derived growth factor (GDNF) and neural growth factor (NGF), and these mediators are fundamental for the maintenance, respectively, of dopaminergic and cholinergic neurons. These factors exert neuroprotection by interfering with the activity of glutamyl transpeptidase gamma and free radicals produced by reactive oxygen species (ROS) and nitric oxide. Furthermore, it is known that the human brain has numerous receptors for vitamin D (VDR), mainly in the hypothalamus and neurons of the substantia nigra. This binding structure is responsible for mediating the biological effects of ^{1,25}(OH), highlighting the importance of this substance in the cognitive functions of individuals and, consequently, in the development of neurodegenerative diseases, such as PD.[5-9]

From this perspective, several studies have highlighted the relationship between vitamin D levels and the development of PD; however, there has yet to be a consensus on the mechanism that triggers this interference. Some authors have demonstrated the influence of abnormal levels of this vitamin in increasing the amount of ultrasensitive C-reactive protein (hs-CRP), with an indirect action of vitamin D being perceived

TABLE — Metadata and content analysis of articles (n = 14)5-17

Authors	Title	Journal	Objectives	Conclusion
de Siqueira et al.[5]	Vitamin D3 actions on astrocyte cells: a target for therapeutic strategy in Parkinson's disease?		Investigate alterations in the vitamin D pathway in astrocytes and neurons and their correlation with ɣsynuclein aggregates in human brains obtained from patients with PD and healthy control patients.	The presence of CYP27B1 astrocytes distinguishes PD patients and suggests their contribution to protecting neurons and improving neuropathological features.
Redenšek et al.[6]	Genetic variability of the vitamin d receptor affects susceptibility to Parkinson's disease and dopaminergic treatment adverse events	Frontiers in Aging Neuroscience	Investigate the association of VDR (vitamin D receptor) genetic variability with the occurrence of adverse events (AEs) from treatment with levodopa and dopamine agonists (DAs) and evaluate whether VDR genetic variability influences the daily dose requirements of dopaminergic treatment necessary to adequately control PD symptoms in an individual patient. Additionally, assess the association between VDR SNPs and the risk of PD in a Slovenian cohort of PD patients.	The study may support a personalized approach to PD treatment, especially in terms of monitoring vitamin D levels and vitamin D supplementation in patients with high-risk VDR genotypes.
Ogura et al.[7]	Circulatory 25(OH)D and 1,25(OH)2D as differential biomarkers between multiple system atrophy and Parkinson's disease patients	eNeurologicalSci	This study aimed to evaluate whether serum 25(OH)D and 1,25(OH)2D can be used as biomarkers to differentiate healthy subjects (HS), multiple system atrophy (MSA), and Parkinson's disease (PD) in patients of both sexes.	Serum 25(OH)D and 1,25(OH)2D could be used as biomarkers for MSA and PD. 25(OH)D and H&Y provided the best sensitivity and group classification by characteristics.
Lien et al.[8]	Correlation between hypovitaminosis D and nutritional status with the severity of clinical symptoms and impaired cognitive function in patients with Parkinson's disease.	Acta Neurologica Taiwan	To evaluate the relationship between the severity of clinical symptoms and cognitive function in patients with Parkinson's disease (PD) and their serum vitamin D levels and nutritional status.	It was revealed that PD patients at risk of malnutrition have impaired cognitive function, but patients with abnormal serum vitamin D levels did not show such an influence. However, PD patients with abnormal vitamin D levels have higher levels of hs-CRP, which affects the cognitive function of PD patients. Therefore, abnormal serum vitamin D levels may have an indirect influence on the cognitive function of PD patients through their effect on hs-CRP levels.
Lv et al.[9]	Assessing the effects of vitamin D on neural network function in patients with Parkinson's disease by measuring the fraction amplitude of low-frequency fluctuation.	Frontiers in Aging Neuroscience	To explore the relationship between Parkinson's disease (PD) levels and vitamin D (VD), as well as to analyze the effects of VD on spontaneous brain activity and investigate the possible mechanisms of its involvement in the risk of PD.	Patients with Parkinson's disease (PD) exhibited lower serum levels of vitamin D (VD) compared to the healthy control group, and VD may have a potential dose-dependent effect on the risk of PD. Lower serum levels of VD may affect spontaneous network neuronal activity in the default mode and visual pathway neurons in PD patients, providing a possible mechanism for its effect on the risk of PD.
Ozturk et al.[10]	Bone mineral density and serum vitamin D status in Parkinson's disease: Are the stage and clinical features of the disease important?	Neurology India	To evaluate the relationship between bone mineral density (BMD) and serum vitamin D levels and the stage or clinical characteristics of Parkinson's disease (PD).	All patients with Parkinson's disease (PD) should be screened for the development of osteoporosis and for sufficient vitamin D levels in the early stages of the disease, as these are related. Preventive methods for bone health should be considered at the onset of PD.
Hiller et al.[11]	A randomized, controlled pilot study of the effects of vitamin D supplementation on balance in Parkinson's disease: Does age matter?	Public Library of Science One, PLoS 1	To explore whether short-term supplementation of high doses of vitamin D is safe and improves balance in individuals with Parkinson's disease (PD).	High-dose vitamin D supplementation in the short term appears to be safe in individuals with Parkinson's disease (PD), but it did not significantly improve balance as measured by the Sensory Organization Test in this pilot study population. A post hoc analysis suggests that vitamin D may have potential to improve balance in a younger population with PD. High-dose vitamin D supplementation in PD requires further studies, especially in light of new research suggesting that megadoses and even moderate doses (as low as 4,000 IU per day) may increase falls in older populations.
Al-Amin et al.[12]	Vitamin D deficiency is associated with reduced hippocampal volume and disrupted structural connectivity in patients with mild cognitive impairment	Human Brain Mapping	Mild cognitive impairment (MCI) is prodromal to neurocognitive disorders, and neuroimaging studies suggest that, in older adults, this cognitive impairment is associated with a reduction in hippocampal volume and structural integrity of white matter. To test whether vitamin D is associated with the neuroanatomical correlates of mild cognitive impairment (MCI), the study analyzed an existing dataset of structural and diffusion magnetic resonance imaging from elderly patients with MCI.	Low vitamin D levels are associated with reduced volumes of hippocampal subfields and connection deficits in older adults with MCI, which may exacerbate neurocognitive outcomes. Longitudinal studies are now needed to determine whether vitamin D can serve as a biomarker for Alzheimer's disease and whether intervention can prevent the progression from MCI to severe cognitive disorders.
Kuhn, Karp e Muller[13]	No vitamin D deficiency in patients with Parkinson's disease.	Degenerative neurological and neuromuscular disease		
Bariche Lv et al.[14]	Clinical correlates of serum 25-hydroxyvitamin D in Parkinson disease	Nutritional Neuroscience	A decrease in vitamin D levels has already been reported in patients with Parkinson's disease, along with correlations to the clinical severity of the disease. This case-control study found higher but not statistically significant plasma levels of 25-OH-vitamin D in patients with Parkinson's disease compared to age- and sex-matched controls, with no association found with clinical parameters such as disease severity scores or cognitive function assessments..	Our results warrant further confirmatory research with a strict matching design between patients and controls, which was not implemented in previous investigations. We emphasize that this case-control study does not allow for any comments on the supposed beneficial effects of vitamin D supplementation, such as on bone mass or bone mineral density, in patients with Parkinson's disease.
Zhang et al.[15]	Relationship between 25-hydroxyvitamin D, bone density, and Parkinson's disease symptoms.	Acta Neurologica Scandinavica	A cross-sectional observational study to investigate whether previous studies were correct in suggesting a negative association between 25(OH)D levels and clinical characteristics of Parkinson's disease (PD), as the data are inconsistent.	Serum 25(OH)D levels were negatively correlated with disease severity and symptoms, as well as with overall cognitive functions. Our study adds evidence that low levels of 25(OH)D may negatively affect the progression of Parkinson's disease (PD). Intervention studies in this area are needed.
Wu et al.[16]	Correlation between serum 25(OH)D and cognitive impairment in Parkinson's disease.	Journal of Clinical Neuroscience	Vitamin D deficiency is widespread in patients with Parkinson's disease (PD). Our aim was to determine whether serum vitamin D levels were correlated with bone mineral density (BMD) and non-motor symptoms in patients with PD..	In patients with Parkinson's disease (PD), vitamin D levels were significantly correlated with falls and some non-motor symptoms. However, no associations were found between bone mineral density (BMD) and serum 25(OH)D levels in patients with PD. Thus, vitamin D supplementation is a potential therapy for the non-motor symptoms of PD..
Marshal et al.[17]	Mechanistic insights into the role of vitamin D and computational identification of potential lead compounds for Parkinson's disease.	Journal of Cellular Biochemistry	This study aimed to investigate the relationship between serum 25(OH)D levels and cognitive impairment in patients with Parkinson's disease (PD), in the hope of providing possible insights for the diagnosis and prevention of PD with cognitive impairment.	These findings support the relationship between cognitive impairment and vitamin D in patients with Parkinson's disease (PD). Serum 25(OH)D may be a useful biomarker for diagnosing cognitive impairment in patients with PD.
Mazzetti et al.[1]	Astrocytes expressing vitamin D-activating enzyme identify Parkinson's disease.	CNS Neuroscience & Therapeutics	The present study aims to evaluate the neuroprotective activity of vitamin D3 in astrocytes following exposure to rotenone (ROT), a natural pesticide known for its neurotoxic potential through the inhibition of mitochondrial complex I.	Therefore, treatment with vitamin D3 protected astrocytes from ROT-induced damage by reducing oxidative stress, decreasing the expressions of NF-kB and Nrf2, and improving mitochondrial function. However, further investigations are needed regarding the involvement and mechanism of action of vitamin D3 in this cellular model of Parkinson's disease (PD), focusing on the crosstalk between Nrf2 and NF-kB.

in the impairment of patients' cognitive functions, as it is capable of acting as an anti-inflammatory factor. However, this function is not perceived in the control of neuroinflammation of microglia. That is, vitamin D deficits do not seem to influence the severity of symptoms but are related to the development of the disease.[8,9,17]

Furthermore, a contribution of astrocytes positive for the vitamin D-activating enzyme (CYP27B1) in neuroprotection was observed. CYP27B1 assists in the second hydroxylation of 25-hydroxyvitamin D into the active metabolite, that is, 1,25-hydroxyvitamin D. These types of astrocytes appear to carry out the uptake and clearance of synuclein, preventing accumulation and sensitization of the dopaminergic neuron to oxidative stress and formation of Lewy bodies. Another aspect noted is the influence of VDR genetic variability on PD susceptibility due to the presence of polymorphisms, such as VDR rs2228570, which has been shown to increase the chances of motor fluctuations, highlighting the role of vitamin D in achieving neuromuscular function.[4,7,10,12-14,18]

Hypovitaminosis can cause a reduction in bone mineral density, proximal muscle weakness, pain, difficulty walking, and postural instability. Therefore, there is evidence of the importance of investigating vitamin D levels in the early stages, to prevent the patient's condition from worsening due to the intense reduction in bone mass as the disease progresses. Supplementation of this vitamin proved to be safe but did not provide considerable improvements in the balance of older patients. However, the possibility of improving balance in young individuals has been reported.[10,12-14]

Vitamin D deficiency in elderly patients with mild cognitive impairment is associated with reduced hippocampal volume and brain structural connectivity. A smaller total hippocampal volume is observed in those with deficient serum 25-OH D levels, which was considered in later studies due to the smaller volumes of the CA1, molecular layer, dentate gyrus, and fimbria subfields. This atrophy occurs through some mechanisms, including increased pro-inflammatory cytokines, increased oxidative stress, reduced level of neurotrophic factors, decreased synaptic protein, and increased excitotoxicity, all of which can result in reductions in subfield volumes of the hippocampus. Disruption of brain structural connectivity in 13 regions has been reported in patients with deficient serum vitamin D levels. Vitamin D improves hippocampal synaptic function in rats. Therefore, disturbances in the structural connectivity of the hippocampus and the reduction in its volume may be related to the loss of synapses and the reduced level of synaptic protein. This low level of synaptic protein is a cause of reduced hippocampal volume, which leads to reduced neuronal connectivity. Network disruption was most evident in the right hemisphere, with the right hippocampus as the center, producing significantly more severe neurocognitive outcomes than patients who were not vitamin D deficient, as reflected in scores from a cognitive battery including MMSE, CDR, CDR-SOB, and GDS.[12]

It is known that increased vitamin D changes blood flow parameters, improving tissue microcirculation. This increases oxygen transport and tissue perfusion, improving mitochondrial function and defense against oxidative stress. As already mentioned, mitochondrial impairment and reduced capacity to eliminate free radicals are closely linked to the pathophysiology of chronic neurodegenerative disorders. Thus, it can be hypothesized that higher vitamin D levels contribute to better coping with PD symptoms, such as cognitive impairment and age-related comorbidities such as diabetes mellitus or cardiovascular diseases.[13]

However, in Kuhn, Karp, and Müller's 2022 case-control study13, they concluded that vitamin D levels did not vary significantly between PD patients and matched controls, and did not show any relationship with the severity of the disease, in contrast to other clinical investigations. However, they report that participants were assessed only once and were not taken off PD medication. Therefore, correlation analysis cannot provide profound value in assessments of functional deficits about vitamin D measurement in this PD cohort.

It is already recognized that patients with PD have reduced serum levels of 25(OH)D when compared to the general population. Furthermore, it was discovered that the deficiency state is mainly associated with reduced sun exposure and food intake, which, in turn, does not appear to be related to the severity of diseases or their progression and cognitive decline. However, the study suggested the existence of confounding factors, as well as endogenous changes in vitamin D metabolism in PD, as serum 25(OH)D levels in PD patients were lower than in controls, even with comparable food ingestion and sunlight exposure. Thus, preliminary evidence suggests that the combination of greater sun exposure and vitamin D supplementation is the most effective strategy, having greater potential benefits from food fortification than dietary modifications alone.[14]

It was also reported that PD patients with low serum levels of 25(OH)D had a higher frequency of falls, sleep problems, depression, and anxiety, in addition to lower BMD in the lumbar spine and femoral neck. Together with the other results, these relationships reinforce that vitamin D deficiency plays a role in the pathogenesis of PD, while vitamin D supplementation can be used to treat the non-motor symptoms of PD.[9]

Furthermore, it has been reported that reduced vitamin D levels may occur in the early stages of the disease, even before its onset. Other studies have found that vitamin D deficiency is present in patients with early, untreated PD. Furthermore, the risk of PD increases significantly as vitamin D levels decrease, and it is important to highlight that this phenomenon is complex and is influenced by several environmental and genetic factors already discussed.[9]

CONCLUSION

The analysis of the scientific productions allowed to conclude that there is no consensus on vitamin D's causal relationship and therapeutic potential in PD. Still, there is strong evidence of its relevance in developing the disease. In this sense, most studies found that the risk of PD increases proportionally to the reduction in serum levels of 25(OH)D, that is, it appears to influence the development of the pathology but is not associated with the severity of the symptoms manifested by the patient. Among the reasons is that vitamin D is capable of modulating neurotrophic factors essential for the maintenance of dopaminergic neurons and even influencing the improvement of tissue microcirculation. Another interesting point is that vitamin D deficiency can occur in the early stages of the disease, demonstrating the importance of investigating levels at the beginning of the disease due to the possibility of reducing bone mineral density and worsening the condition due to falls. Although vitamin D has not demonstrated benefits in improving the balance of older patients, benefits have been seen from administering a moderate dose in young individuals; however, it is essential to carry out other studies on the causal relationship and therapeutic possibilities of the corresponding vitamin D.

Author´s contribution

Nicole Custódio Porto Silva: Formal analysis, Methodology
Rafael badalotti: Project administration
Laís Gabriel Inácio da Silva Dantas: Data curation, Writing – original draft
Nathália Carolinne Rabêlo de Souza: Validation, Writing – review & editing

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Multidisciplinary approaches in skull base surgeries for pituitary tumors

Abordagens multidisciplinares em cirurgias da base do crânio para tumores hipofisários

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ABSTRACT

Introduction: Skull base tumors present considerable clinical challenges due to their complex location, often resulting in significant morbidity during treatment.

Objective: To review current management techniques, including surgical and radiation therapies, the evolution of treatment approaches, and emerging technologies such as augmented reality and proton therapy.

Method: A narrative review was conducted to identify the main multidisciplinary strategies in the treatment of pituitary tumors.

Result: Traditionally, disease control has been based on surgical resection and radiation therapy, with accessibility issues complicating treatment strategies. These tumors arise from various anatomical structures, including bony tissues, cranial nerves, and the pituitary gland, requiring a multidisciplinary approach involving specialists such as neurosurgeons, radiation oncologists, and otolaryngologists. Pituitary tumors, accounting for 16.7% of skull base tumors, exhibit varying clinical impacts depending on their functional status.

Conclusion: The findings emphasize the need for collaborative approaches and the integration of innovative technologies to improve outcomes for patients with skull base tumors.

KEYWORDS: Skull base tumors. Pituitary tumors. Multidisciplinary approach. Surgical management. Radiation therapy. Augmented reality. Proton therapy.

Central Message

The management of skull base tumors, particularly pituitary tumors, requires a multidisciplinary approach due to their complex anatomic location, which significantly impacts treatment outcomes and patient prognosis.

Perspective

As skull base tumors become increasingly prevalent, understanding the intricate interactions between surgical, medical, and radiation oncologic techniques is essential. This article emphasizes the importance of collaborative efforts among multiple specialists to improve patient care and optimize treatment strategies.

RESUMO

Introdução: Os tumores da base do crânio apresentam desafios clínicos consideráveis devido à sua localização complexa, muitas vezes resultando em morbidade significativa durante o tratamento.

Objetivo: Revisar as técnicas atuais de manejo, incluindo terapias cirúrgicas e de radiação, a evolução das abordagens de tratamento e tecnologias emergentes, como realidade aumentada e terapia de prótons.

Método: Foi realizada uma revisão narrativa para identificar as principais estratégias multidisciplinares no tratamento dos tumores hipofisários.

Resultado: Tradicionalmente, o controle da doença tem sido baseado na ressecção cirúrgica e na radioterapia, com problemas de acessibilidade complicando as estratégias de tratamento. Esses tumores surgem de várias estruturas anatômicas, incluindo tecidos ósseos, nervos cranianos e glândula pituitária, exigindo uma abordagem multidisciplinar envolvendo especialistas como neurocirurgiões, oncologistas de radiação e otorrinolaringologistas. Os tumores hipofisários, responsáveis por 16,7% dos tumores da base do crânio, apresentam impactos clínicos variados dependendo de seu estado funcional.

Conclusão: Os achados enfatizam a necessidade de abordagens colaborativas e a integração de tecnologias inovadoras para melhorar os resultados para pacientes com tumores da base do crânio.

PALAVRAS-CHAVE: Tumores da base do crânio. Tumores hipofisários. Abordagem multidisciplinar. Manejo cirúrgico. Radioterapia. Realidade aumentada. Terapia de prótons.

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INTRODUCTION

Skull base tumors pose a significant clinical challenge due to their intricate location, often resulting in substantial morbidity during treatment. Surgical resection, radiation therapy, or a combination thereof has traditionally been employed for disease control. However, the accessibility of these tumors and their proximity to critical structures may limit therapeutic options. They constitute a heterogeneous group arising from diverse anatomical structures, including bony structures, cranial nerves, meninges, sinonasal tract, pituitary gland, and embryonic tissues. Addressing these tumors requires a multidisciplinary approach involving specialists such as radiation oncologists, medical oncologists, neuro-oncologists, neurosurgeons, otolaryngologists, and head and neck surgeons. Treatment strategies have traditionally focused on surgical resection supplemented by radiation therapy, and occasionally, chemotherapy or targeted therapy.[1]

Pituitary tumors, with an average incidence of 16.7%, emerge as a prevalent subset of skull base tumors. Their clinical impact varies, with functioning tumors causing early symptoms and nonfunctioning ones reaching considerable size before becoming symptomatic. Surgical evolution in pituitary tumor management reflects diagnostic and surgical advancements in neurosurgery, emphasizing the importance of comprehensive knowledge of surgical skull base anatomy. Despite progress in medical and radiation treatments, surgery remains the primary therapeutic modality, aiming for visual improvement, hormonal cure, and prevention of hypopituitarism and neurological deficits.[2]

Various transcranial approaches, including midline, anterolateral, and lateral, have been proposed for the safe resection of craniopharyngiomas. The initial assessment of adult patients with craniopharyngiomas necessitates a comprehensive evaluation, encompassing clinical, endocrinological, ophthalmological, radiological, and neuropsychological aspects.[3]

For most patients, transsphenoidal surgery emerges as the optimal primary treatment for craniopharyngiomas. The choice between endoscopic and microscopic approaches currently relies on the surgeon's expertise and preference, with further studies required to establish comparative outcomes. Craniotomy is rarely indicated in acromegaly cases, and investigational techniques, such as intraoperative MRI, aim to enhance visualization of tumor remnants during surgery.[4]

This article will analyze the contribution of multidisciplinary approaches in the effective treatment of skull base tumors, involving specialists such as radiation oncologists, medical oncologists, neuro-oncologists, neurosurgeons, otolaryngologists, and head and neck surgeons. It also seeks to investigate different transcranial approaches, such as those targeted at craniopharyngiomas, and assess their effectiveness and safety in the context of tumor resection.

By addressing these objectives, this article aims to provide a comprehensive and updated insight into the state of the art in skull base tumor management, contributing to advances in the understanding and treatment of these challenging diseases.

METHOD

The present study is a narrative review that explored the DeCS/MeSH descriptors "skull base surgery", "pituitary tumors", and "multidisciplinary approaches" to address the guiding question: "What are the main multidisciplinary approaches in skull base surgery for pituitary tumors, and how does their effectiveness impact patient prognosis?" The following databases were utilized: PubMed, ScienceDirect, and BVS, following inclusion criteria, which included articles in English, Portuguese, or Spanish, with full-text availability, and relevance to the guiding question. The time frame considered was from 1998 to 2023.

RESULT

A total of 117 articles were identified. The articles discussed implications for individual patient health undergoing surgery, long-term neurological outcomes, prognosis of patients treated through this approach, and the key multidisciplinary strategies associated with skull base surgery for pituitary tumors. Ultimately, 100 articles were analyzed, and 16 selected to compose this review.

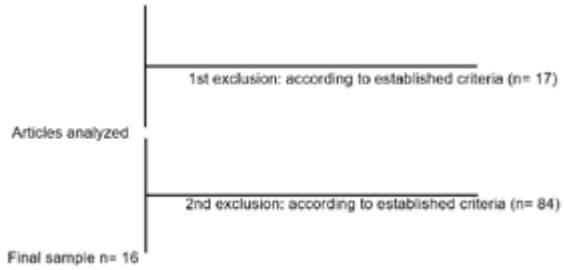

FIGURE - Flowchart of articles selected in the review identified in databases PubMed, ScienceDirect and BVS

DISCUSSION

The gold standard approach for pituitary adenomas is endoscopic endonasal transsphenoidal surgery, a complex procedure which is not very probable to achieve complete resection of the tumor, especially in giant pituitary neuroendocrine tumors (studies report that a gross total resection of the pituitary adenoma is obtained in less than half of the surgeries).[5-7] A retrospective study6 showed remission rates of surgical interventions for PAs. ACTH-releasing adenomas are more responsive, obtaining about 80% of remission only with surgery. Adding complementary surgery and stereotactic radiation surgery to the treatment increased the rate to 94%. GH-producing adenomas did not show the same responsiveness, representing a rate of 60% of remission with primary, revision and stereotactic radio surgeries. An important limitation of this surgical approach is the high possibility of cerebrospinal fluid leakage and infections, such as meningitis.[5] Reconstruction techniques of skull base defects are required to avoid further complication in the postoperative. There are not standard surgical procedures until the present moment, but synthetic (titanium, silicone) and autologous (fascia lata,

paraumbilical fat) tissues are commonly used for sellar and dural reconstruction, although they have potential probability of collateral effects and complications, such as infections and risk of foreign body reactions. Besides that, most of those procedures are difficult to shape and can have a high complexity. For example, although fragments of autologous bones have no risk of rejection, they usually are obtained in irregular sizes and borders, hampering the reconstruction.[8-10]

Alternative and complementary therapies have been studied to enhance the treatment and the surgical techniques of tumors located near the skull base, such as pituitary adenomas. One of the alternatives is the introduction of intraoperative instruments to enhance neuronavigation systems and, therefore, to obtain a superior accuracy of the lesions.[11,12] Traditional neuronavigation systems have some limitations that hamper the obtaining of highly accurate 2D images preoperatively.[13] To overcome these limitations, 3D technologies are being studied as alternatives, such as augmented reality, an advanced tool that superimposes virtual objects images generated in computer systems, such as CT or MRI, providing a direct view of the spatial anatomy and enabling the visualization of blood vessels and boundaries of the area through a microscope, tablet, smartphones and others displays types.[13-15] A cohort study Zhang et al.[13] that, comparing surgeries with augmented reality support and surgeries based on classical approach, the overall duration of the surgery and complication rates had not a considerable difference. However, preparation time was significantly longer in surgeries with the augmented reality technology due to the set up for surface-based or intraoperative CT-based registration. This finding could also be related to the familiarity of the surgical team to the technologies being used. So, augmented reality is a promising technology which facilitates surgical orientation, especially in cases where a patient has anatomical variants, and also is a support in the process of training surgical orientation residents and surgeons at the beginning of their career, improving skills in transsphenoidal approach.[12] 3D-printing technology is another promising technology that also helps to obtain a high anatomical accuracy, such as the morphology of the sellar floor, the orientation of blood vessels and arteries at the sella turcica area improving the transsphenoidal surgical procedure and outcomes.[14] A retrospective study by Colli et al.[14] demonstrated that the use of 3D-printing technology reduced the operation time, blood loss and postoperative complications, indicating a favorable alternative for the surgical treatment of tumors in regions with a complex anatomical structure, such as pituitary adenomas.

Alkylating chemotherapeutics also have been studied as an alternative to the treatment of aggressive pituitary adenomas. Authors reported the results of a study where the sample of patients (diagnosed with pituitary carcinomas or aggressive pituitary adenomas) were treated with temozolomide as a first-line chemotherapy agent at a mean duration of 9 months.[15] About 40% of the sample showed a radiographic response, and less than 10% had complete regression of the tumor. Another significant finding is that non-functioning pituitary adenomas had a minor response compared to hormonally functioning tumors. A better radiographic response was also found in patients that had lower activity rates of the O6-methylguanine methyltransferase (MGMT), similar to what occurs in glioblastoma cases.

Gene therapy using intracellular signaling pathways and targeting growth factors (directly or their receptors) is another promising alternative conduct. Inhibitors of Raf/Mek/erk and PI3K/Akt/mTOR pathways (important in the regulation of cell proliferation/growth and its expression is discovered to be elevated in pituitary tumors) showed a reduction in aggressive pituitary adenomas in murine models, but clinical studies are still limited in this area.[15,16] Besides that, authors[15] reported no success in the use of Everolimus (the only PI3K/AKT/mTOR pathway inhibitor with available studies in humans) as second/third line monotherapy in a sample. Meanwhile, was exposed that *in vitro* studies with Everolimus induced cell apoptosis, suggesting a possible alternative in the treatment of invasive and recurrent non-functioning pituitary neuroendocrine tumors16 As for hormonally active pituitary adenomas, EGFR TKI inhibitors demonstrated a role in the regulation of tumoral growth and hormonal secretion.[16] Another medication, vemurafenib (BRAF inhibitor) exhibits less ACTH expression when used in murine models. However, this mutation only is present in corticotroph pituitary adenomas with BRAF mutation.[15] Oral lapatinib, an inhibitor of EGFR and HER2, showed a significant reduction of tumor prolactin expression (around 80%), indicating an alternative in treating refractory prolactinomas, since prolactin levels were elevated in transgenic EGFR/HER2 murine models.[16]

Proton therapy is also an alternative to the standard treatment of skull base tumors, as pituitary adenomas, presenting the advantages to target the tumor more accurately, at the same time that it protects adjacent tissues and to limit long-term side effects. Especifically for pituitary adenoma cases, radiotherapy is an usual and effective treatment to prevent residual tumor growth. However, this approach has the potential to develop a series of adverse effects, especially in young patients, wherein radiation-induced second malignancy is more probable to occur.[17] A retrospective study showed that, in a sample in which patients (diagnosed with functional pituitary adenomas) were treated with proton stereotactic radiosurgery in a median dose of 20 Gy(RBE), proton stereotactic radiosurgery reduced-dose in patients that had previous radiation treatment or with fractionated stereotactic proton radiation therapy the median time do biochemical complete response were around 60% and 30 months for Cushing's disease or Nelson syndrome patients and around 25% and 60 months for prolactinoma or acromegaly cases. Tumor control was almost 100% in 85% of the cases, indicating that proton therapy is an effective alternative for functional pituitary adenomas.[18] Nonetheless, hypopituitarism is a relatively common adverse side effect of the proton irradiation therapy (around 60%).[18] Pencil-beam scanning proton therapy is an promising alternative for future studies, since

it can shield an amount of volume to preserve pituitary function, while targeting the tumoral part.[17]

CONCLUSION

The approach to skull base tumors represents a significant challenge due to their intricate location, often resulting in considerable morbidity during treatment. Surgical resection, radiation therapy, or a combination thereof has traditionally been employed for disease control. However, the accessibility of these tumors and their proximity to critical structures may limit therapeutic options. They constitute a heterogeneous group arising from diverse anatomical structures, including bony structures, cranial nerves, meninges, sinonasal tract, pituitary gland, and embryonic tissues. A multidisciplinary approach for the effective treatment of these complex tumors is necessary. Treatment strategies have traditionally focused on surgical resection supplemented by radiation therapy, and occasionally, chemotherapy or targeted therapy. Specifically, pituitary tumors emerge as a prevalent subset of skull base tumors. The surgical evolution in pituitary tumor management reflects diagnostic and surgical advancements in neurosurgery, emphasizing the importance of comprehensive knowledge of surgical skull base anatomy. Although medical and radiation treatments have progressed, surgery remains the primary therapeutic modality aiming for visual improvement, hormonal cure, and prevention of hypopituitarism and neurological deficits.

Contribuição dos autores

Rafaela Fernandes Gonçalves: Project administration
Marisa Bezerra de Araújo: Validation, Writing – review & editing
José Pedro Delgado: Data curation, Writing – original draft
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Advances in artificial intelligence, robotics and augmented virtual reality in neurosurgery

Avanços em inteligência artificial, robótica e realidade virtual aumentada em neurocirurgia

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ABSTRACT

Introduction: Innovations in artificial intelligence (AI) and technology have revolutionized neurosurgery, a complex specialty where precision is crucial. Application areas include spinal, vascular, epilepsy, tumor, functional, trauma, and critical care neurosurgery. Notable advancements include robot-assisted minimally invasive surgery, telemedicine, telesurgery, and augmented/virtual reality, which enhance treatment precision and neurosurgeon training.

Objective: To review the recent advances in IA applicable to neurosurgery.

Method: The research question was defined as: "What are the main technological advancements in neurosurgery and their importance in surgical practice?" Using English MeSH descriptors, searches were conducted in the PubMed, Medline, and Science Direct databases. Original studies in English or Spanish addressing the question were included, excluding duplicate, review articles, and those outside the scope.

Result: Studies demonstrate the diverse application of AI in neurosurgery, mainly in neuro-oncology, functional, vascular, spinal, and traumatic brain injury surgery. AI enhances diagnosis, surgical planning, and postoperative monitoring, increasing the precision and safety of interventions. AI also aids in diagnosing conditions like intracerebral hemorrhage, though challenges such as false positives and the need for medical confirmation persist.

Conclusion: Technological innovations in AI, robotics, and augmented reality/ virtual reality are redefining neurosurgery, enhancing the precision, safety, and efficacy of treatments. Telemedicine and telesurgery expand access to specialized care, while professional training is improved with new training tools. Collaboration between the medical community and regulators is essential to maximize the benefits of these innovations.

KEYWORDS: Neurosurgery. Artificial intelligence. Robotics. Augmented reality. Virtual reality.

RESUMO

Introdução: As inovações em inteligência artificial (IA) e tecnologia revolucionaram a neurocirurgia, uma especialidade complexa onde a precisão é crucial. As áreas de aplicação incluem neurocirurgia espinhal, vascular, epilepsia, tumoral, funcional, trauma e cuidados intensivos. Avanços notáveis incluem cirurgia minimamente invasiva assistida por robô, telemedicina, telecirurgia e realidade aumentada/virtual, que aumentam a precisão do tratamento e o treinamento do neurocirurgião.

Objetivo: Revisar os recentes avanços na IA aplicáveis à neurocirurgia.

Método: A questão de pesquisa foi definida como: "Quais são os principais avanços tecnológicos em neurocirurgia e sua importância na prática cirúrgica?" Usando descritores MeSH em inglês, foram realizadas buscas nas bases de dados PubMed, Medline e Science Direct. Foram incluídos estudos originais em inglês ou espanhol abordando a questão, excluindo artigos duplicados, de revisão e aqueles fora do escopo.

Resultado: Estudos demonstram a aplicação diversificada da IA em neurocirurgia, principalmente em neuro-oncologia, cirurgia funcional, vascular, espinhal e traumatismo cranioencefálico. A IA aprimora o diagnóstico, o planejamento cirúrgico e o monitoramento pós-operatório, aumentando a precisão e a segurança das intervenções. A IA também ajuda no diagnóstico de condições como hemorragia intracerebral, embora persistam desafios como falsos positivos e a necessidade de confirmação médica.

Conclusão: As inovações tecnológicas em IA, robótica e realidade aumentada/realidade virtual estão redefinindo a neurocirurgia, aumentando a precisão, segurança e eficácia dos tratamentos. A telemedicina e a telecirurgia ampliam o acesso ao atendimento especializado, enquanto a formação profissional é aprimorada com novas ferramentas de treinamento. A colaboração entre a comunidade médica e os reguladores é essencial para maximizar os benefícios dessas inovações.

PALAVRAS-CHAVE: Neurocirurgia. Inteligência artificial. Robótica. Realidade aumentada. Realidade virtual.

Central Message

The article explores how advances in artificial intelligence, robotics, and augmented/virtual reality are revolutionizing the field of neurosurgery. These technological innovations are significantly improving the accuracy, safety, and efficacy of neurosurgical procedures, as well as expanding access to specialized care through telemedicine and telesurgery. In addition, these technologies are enhancing the training and education of neurosurgeons by providing more realistic and effective learning tools.

Perspective

The integration of AI, robotics, and augmented/virtual reality into neurosurgery represents a transformative shift in the medical field. While these technologies offer tremendous potential to improve patient outcomes and optimize surgical practices, the article emphasizes the importance of addressing ethical, regulatory, and technology adoption challenges. Ensuring the safe and effective application of these innovations requires ongoing collaboration between the medical community and regulatory bodies. By overcoming these challenges, the full benefits of these advances can be realized, leading to improved quality of care and improved patient outcomes.

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INTRODUCTION

The innovations in the field of technology and artificial intelligence (AI) in recent decades have played a crucial role in the revolution of medicine, particularly benefiting neurosurgery — a highly complex and sensitive specialty where precision and quality of treatment are crucial for better disease management. The main areas of application for these techniques within the neurosurgical spectrum include spinal neurosurgery, vascular neurosurgery, epilepsy surgery, tumor surgery, functional neurosurgery, trauma, and surgical intensivism.[1]

A remarkable example of this transformation is the approach to intracerebral hemorrhage, a critical condition with high morbidity and mortality rates. Among the tools developed for managing such cases, surgical robots used in minimally invasive surgeries offer the prospect of more precise and effective treatments.[2] The application of AI in radiology has also shown promise in detecting serious conditions such as intracerebral hemorrhage; however, false positives persist.[3]

Other advances, available in a lot of medical specialties, such as telemedicine, telesurgery, and tele-guidance, have allowed surgeons to collaborate remotely and guide learners in real-time, expanding the possibilities for medical assistance and neurosurgery training.[4] The benefits of this resource became evident during the Covid-19 pandemic, demonstrating its potential for improving access to surgical care in remote locations. Limitations regarding data quality and device availability must be considered.[5]

In addition to technical improvements, quinquennial attention has gained importance in the specialty, as performing long and repetitive procedures can physically overwhelm professionals. Thus, the introduction of robotics with exoscopes and portable devices has enhanced ergonomics in the operating room, minimizing the physical effort and fatigue of surgeons.[6]

The integration of augmented reality (AR) and virtual reality (VR) in neurosurgery has also allowed progress. While AR integrates virtual information generated through computational resources into the physical world, VR acts antagonistically by immersing the user in the computational world. These tools provide surgeons with an enhanced view of the operating field and the ability to perform interventions more precisely.[7-9]

Nevertheless, it is essential to recognize that these new approaches present significant obstacles, including the requirement to overcome the limitations of current surgical robots, ensure the safety of AI, be accessible, and address ethical issues related to automation in medicine. Furthermore, proper training of the involved physicians is necessary.[10]

This article aims to explore and highlight the notable advancements in AI, robotics, AR, and VR related to neurosurgery. The fundamental purpose is to address how these technological solutions are enhancing treatment accuracy, expediting diagnoses, and providing more effective training opportunities for neurosurgeons, offering a comprehensive view of the field, emphasizing its benefits and drawbacks, and demonstrating how they are shaping the future of neurosurgery in the pursuit of more satisfactory outcomes for patients.

METHOD

Initially, the theme "Advances in neurosurgery related to artificial intelligence, robotics, and augmented reality" was established. Subsequently, the guiding question "What are the main technological advances in neurosurgery, and what is the importance of this evolution in improving surgical practice?" was defined.

The search strategy involved using English descriptors registered in the Medical Subject Headings (MeSH): "Artificial intelligence," "Robotics," "Augmented virtual reality," and "neurosurgery." For scientific foundation, searches were conducted on PubMed, Medline (BVS), and Science Direct databases, using the boolean operator "OR" to associate descriptors in the search.

Search results were selected based on inclusion and exclusion criteria applied to full-text articles. Only original studies related to the theme that addressed the guiding question, in English or Spanish, were included. Duplicated articles, review articles, and those not fitting the scope of this review were excluded. At the end 25 articles were included in this review.

RESULT

The metadata, objective and results of articles included in this review are disposable through the QRCode or link bellow.[1-26]

Supplementary file

DISCUSSION

The review of studies on the use of AI in neurosurgery reveals that its utilization presents various promising applications, particularly in areas such as neuro-oncology, functional neurology, vascular neurosurgery, spinal neurosurgery, and traumatic brain injury surgery. It contributes to improved diagnostic accuracy, surgical planning, intraoperative interventions, and postoperative monitoring, leading to greater success in surgical approaches and better prognoses for patients.[1] However, there are notable challenges to the adoption of AI in surgical practice, including ethical considerations, the need for further research and model training for widespread application, and the necessity of interdisciplinary collaboration.

The combination of AI with neuroimaging has resulted

in increased diagnostic accuracy in neurosurgery, particularly regarding brain tumors, intracranial aneurysms, traumatic injuries, and other conditions. AI has demonstrated high performance in diagnosing intracerebral hemorrhage, with high precision, sensitivity, and specificity, promising improvements in patient care.[11] It has also shown promise in detecting non-ruptured intracranial aneurysms through computed tomography angiography, significantly increasing sensitivity and precision, and promoting greater agreement among physicians in interpreting computed tomography angiography for diagnosis.[12] Furthermore, AI has proven effective in detecting degenerative spinal conditions from X-ray images, enabling early and more accurate diagnoses with the potential to enhance condition management.[13]

However, AI diagnosis of intracerebral hemorrhage may produce false positives, particularly postoperatively, where false positives are more frequent.[3] Additionally, difficulties have been observed in AI detecting lesions with hematomas due to the diffuse margin between edema and hematoma. Therefore, while promising, specific challenges must be overcome by AI to improve its diagnostic accuracy and clinical utility. In some cases, the subjective analysis of a medical professional, careful reviews, and occasionally additional tests are still recommended to confirm the AI interpretation.

Nevertheless, the use of AI would be of great value in reducing the time and cost of diagnoses, prioritizing exams with a higher probability of diseases for analysis by the medical team, leading to more efficient treatment and better prognoses for patients.

AI has also made significant strides in improving surgical planning, making it more precise and personalized, resulting in greater success in surgeries. Through the analysis of medical images from databases, AI can identify critical areas and recommend more suitable surgical approaches for each patient, leading to greater procedural efficiency, shorter surgery times, and, consequently, a reduction in related risks, preserving healthy brain structures. The use of augmented reality applied to technologies such as HoloLens can integrate MRI images to evaluate the surgical procedure.[14] Thus, the use of AI is associated with greater success and safety in the surgical process, reducing complications.

Telemedicine, driven by the application of AI, has demonstrated effectiveness and is well-received by patients and doctors, proving useful for remote tracking and accurate diagnoses. This application has been indicated as possibly effective in screening for pediatric craniosynostosis, where the combination of AI, image processing, big data, and machine learning allowed for high-accuracy telemedicine diagnosis, sensitivity, and specificity.[5] Combining telemedicine with AI could reduce costs (due to its easy application), facilitate population access to medical care (especially in remote regions), enable earlier disease diagnosis, improve outcomes in neurosurgery practice, and enhance interpretation capabilities for non-specialists in the field.

On the other hand, tele-surgery is a system where a surgeon can perform a surgical intervention from a remote location, using surgical robots. This allows for remote surgeries and surgical consultations, expanding access to specialists in distant locations. The introduction of minimally invasive robotic surgery, also known as telerobotics, where surgeons oversee semi-automatic systems remotely, has driven the concept of remote surgery. In addition to telerobotics, a concept also employed in tele-surgery is telepresence, which allows patients and doctors to feel present in remote locations through detection and display technology.[4]

In addition to telesurgery and telemedicine, an innovation that demonstrates great potential for improving medical education, the development of professionals, and an increase in the quality of patient care by medical and surgical teams is the possibility of communication between experts, mentors, and the physicians responsible for patient care in rare and complex procedures. This allows for greater sharing of knowledge and guidance, along with practical training, enabling enhanced skills development for these professionals.[15] However, there are still limitations and ethical challenges, such as varying regulations in different states and countries, and a lack of clear regulation for telemedicine, tele-mentoring, and tele-surgery, raising important concerns that need to be analyzed, debated, and legally regulated for further advancements in the field.

The use of AI during surgical procedures also shows great promise, such as the precise localization of lesions and the use of technologies like augmented reality that assist neurosurgeons and their teams in executing operations. Improved visualization of structures, including 3D and modular visualization, can be employed to meet the specific needs of each surgery. This includes enhancing 3D surgical video flow through the use of modular features, utilizing 3D cameras and sensors, and incorporating depth information into the surgical video flow.[8] Additionally, the use of previously mentioned technologies like Google Glass and Microsoft HoloLens allows for greater success in surgeries due to enhanced surgical education related to the visualization of neuroimages during the surgical procedure.[14] These technologies enable surgeons to decide the best method for image visualization in surgeries, adapting the technologies used based on the complexity of the procedure, offering flexible and promising solutions to improve visualization and precision in 3D surgeries.

However, achieving a perfect 3D view is a challenging task, especially in surgeries involving deformable tissues, indicating an urgent need for improvement in 3D vision and AI in AR systems. Nevertheless, the development of the theory of parallel intelligence in AR systems represents a significant advancement with the potential to significantly increase the efficiency and effectiveness of surgical procedures and medical treatments.[7] Due to its ability to enhance spatial perception and provide additional

information during medical procedures, the use of parallel intelligence in AR represents notable progress in the healthcare field.

The use of other methods to enhance the visualization of structures during surgery with the assistance of AI, particularly in vascular structures, has also made significant strides. In neurosurgery, the treatment of intracranial aneurysms using the microscopic intracranial clipping method is considered the preferred technique, but due to potential complications, the use of indocyanine green angiography combined with AI application in the form of the Otsu method is proposed. This allows for real-time image segmentation, providing an enlarged and clearer view of vascular structures, such as the aneurysm and its peripheral vessels.[16] The use of AI-based visualization methods allows for greater precision and success in surgery, reduced postoperative complication rates, improved prognosis and quality of life, and better treatment for patients with this condition.

Simultaneously, regarding the challenges posed by surgeries involving deformable tissues, the significant need for accurate real-time prediction of deformation in neuroimage-guided surgeries has stimulated the development of a real-time tissue deformation modeling approach.[17] The proposed method involves combining precomputed simulations using the Finite Element Method with machine learning algorithms to create patient-specific deformation models. A brain tumor was used as a model object, and the simulation results were used to train algorithms (artificial neural networks and support vector regression) to predict real-time deformation. The conclusions of the article demonstrate that it is possible to accurately predict tumor deformation (or any other type of soft tissue) in real-time, providing relevant information about anatomy and load during surgery. Its use is suitable for high-fidelity AR systems, offering high patient specificity and fewer errors compared to previously employed methods.

Furthermore, technological advancements in surgical instruments and the ergonomics of surgeons also contribute to better outcomes in neurosurgical procedures. Improvements in materials for minimally invasive surgical techniques have the potential to revolutionize this type of operation. For example, the development of flexible and thermally programmed beveled-tip needles resulted in the miniaturization of complex needle structures, increasing precision and versatility in their use.[18] In the context of minimally invasive surgeries, the development of robotic surgery is a promising innovation in various aspects of neurosurgery, such as the treatment of intracerebral hemorrhage, where it shows lower recurrence rates, improved neurological function, and lower rates of intracranial infection. Proposals for creating robots that can adapt and interact in complex environments, collaborating with doctors and patients, such as the Tri-Co Robot, would improve the precision, individualization, and standardization of intracerebral hemorrhage treatment.[2]

Additionally, the development of ergonomic materials for neurosurgeons, such as the aforementioned robotic surgery, the exoscope, and other manually operated instruments with greater freedom of movement, facilitates surgical procedures, reducing excessive effort and joint and muscle tension. This has the potential to reduce musculoskeletal disorders, fatigue, and effort for surgeons and the team in the future.[6]

From another perspective, the development and significant potential of robotic surgery indicate its crucial future importance, particularly in the field of neurosurgery. This consequently necessitates the training of neurosurgeons in this type of surgical approach. However, the learning process still has various deficiencies, such as the lack of a standardized method. Hence, it can benefit from the use of 3D-printed hydrogel models and AI to enhance this process, providing a realistic anatomical representation for ethical and cost-effective surgical technique training. The use of AI enables the assessment of the doctor's performance during surgical training by collecting, processing, and analyzing data obtained throughout the process, providing feedback to the professional, improving decision-making, and surgical planning.[19] Moreover, AI can play a role in telementoring, performance measurement, eye tracking, and analysis of task-evoked pupil responses. Thus, the use of AI and 3D hydrogel models is very promising, with the potential to enhance robotic surgery training, improve the technical skills of professionals, and ensure greater patient safety.

It is also necessary to assess the microsurgical skills of neurosurgeons, and with the advancement of AI, promising tools are being developed for the objective and automated evaluation of these surgical skills. Through a vision-based framework, AI uses deep learning techniques to detect surgical tools, locate their coordinates, and track their movement in surgical videos, avoiding bias induction as seen in traditional methods or limitations found in tool-tracking-based methods.[20] The results indicate that the framework achieved high accuracy in differentiating between expert and novice surgeons, demonstrating a significant potential for implementation on a larger scale in the future.

AI also holds great promise for application in post-surgical monitoring and postoperative patient recovery, where it has proven effective in the early detection of postoperative complications. This allows the medical team to intervene more quickly, resulting in better outcomes and recovery, leading to an improved prognosis for the patient. The ability of AI to analyze continuous data such as vital signs and alert the team to relevant changes in the patient's condition is crucial in post-surgical monitoring.

In post-surgical recovery, AI can complement commonly used methods with limitations (such as drug therapy and physiotherapy), leading to a proposal for AI and virtual reality based rehabilitation. The rehabilitation methodology combined with AI and

VR showed a significant improvement compared to traditional methods due to the ability to adjust and track exercises and activities, allowing for the personalization of the rehabilitation process and real-time feedback. This also contributed to the improvement of the emotional state of the evaluated patients.[9] Thus, it is concluded that this rehabilitation model is effective and promising, with significant clinical value, although it presents a high cost and requires further research and development of VR technologies for future widespread clinical application.

The application of AI and advanced technologies in medicine brings numerous positive perspectives for medical and surgical practice. However, these innovations are not without challenges and limitations that need to be carefully addressed. The integration of AI into medicine offers promising opportunities, but also raises issues related to data quality, result interpretation, security, resistance to adoption, and understanding the human context. While most surgeons and surgical teams recognize the tremendous potential of AI applied to medical practice, they also express reservations and concerns about its use, particularly regarding the loss of human touch, the need for retraining of these professionals, and its use in postoperative management.[21]

Addressing these challenges requires a thoughtful and careful approach involving healthcare professionals, researchers, and regulators to ensure that AI is applied ethically, safely, and effectively in medical and surgical practice, thereby having the potential to significantly improve patient care, prognosis, and the performance of the medical team.[15]

CONCLUSION

The technological advancement in neurosurgery, driven by AI, robotics, augmented and virtual reality, is redefining the medical landscape, providing significant benefits. As mentioned in a recent study, AI is transforming diagnostic accuracy, surgical planning, and intraoperative intervention, substantially improving surgical outcomes. Telemedicine, telementoring, and tele-surgery, coupled with AI, are expanding access to quality healthcare, especially in remote locations. These approaches offer innovative solutions but face legal and ethical challenges that require careful regulations. In the context of surgery, AI is enhancing 3D visualization, improving the accuracy of surgical interventions. Post-surgical monitoring and post-operative recovery benefit from AI, with early detection of complications These approaches promise to improve patients' quality of life. However, the promises of AI in neurosurgery come with challenges. Ethical, regulatory issues, and the need to balance technology with the human touch in medicine must be carefully addressed, In this regard, it is essential for the medical community and regulators to collaborate to ensure that AI and advanced technologies continue to enhance medical practice while maintaining a focus on patient care quality. Ultimately, the future of neurosurgery is being shaped by these innovations, which have the potential to elevate the precision, efficiency, and safety of procedures, with evident benefits for patients. The responsible integration of AI in neurosurgery is the path to achieving more satisfactory outcomes for patients and advancing the field of medicine.

Author´s contribution

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Viviane Aline Buffon: Validation, Writing – review & editing
Isabela Alves Raymundo: Data curation, Writing – original draft
Julia Dias Guimarães Silva: Conceptualization, Investigação
Isabella Maria Nery Silva: Formal analysis, Methodology
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DREZotomy approach in the management of neuropathic pain

Abordagem de DREZotomia no manejo da dor neuropática

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ABSTRACT

Introduction: DREZotomy is a type of neurosurgical treatment for pain that involves lesions in the dorsal zone of the spine, interrupting the transmission of nociceptive neural stimuli. The main indications are related to oncologic pains resistant to morphine and some cases of neuropathic pain that meet surgical criteria.

Objective: To conduct a literature review to identify the effectiveness of DREZ surgery for patients with neuropathic pain and to report the consequences of this type of treatment.

Method: As a search strategy, English descriptors registered in the Medical Subject Headings (MeSH) were used. For scientific support, searches were conducted on the PubMed, Medline (BVS), and Science Direct databases using the Boolean operator "OR" to associate the descriptors in the search.

Result: The lesion of the dorsal root entry zone (DREZ) is still used as a treatment option for some painful conditions, as well as for spasticity in selected patients. The most commonly techniques for performing DREZotomy are microsurgical and radiofrequency coagulation DREZ. Technical difficulties in using punctures to perform radiofrequency lesions include complications such as injuries to the dorsal columns or the corticospinal tract.

Conclusion: DREZotomy is an effective therapeutic option for relieving neuropathic pain in various clinical contexts. However, it is important to note that pain relief can vary among different types of conditions, with generally higher success rates in patients with nerve root avulsion and brachial plexus injuries.

KEYWORDS: DREZotomy. Surgery. Neuropathic pain.

Central Message

DREZotomy is a type of neurosurgical treatment for pain that involves lesions in the dorsal zone of the spine, interrupting the transmission of nociceptive neural stimuli. The main indications are related to oncologic pains resistant to morphine and some cases of neuropathic pain that meet surgical criteria.

Perspective

DREZotomy is an effective therapeutic option for relieving neuropathic pain in various clinical contexts. However, it is important to note that pain relief can vary among different types of conditions, with generally higher success rates in patients with nerve root avulsion and brachial plexus injuries.

RESUMO

Introdução: A DREZotomia é um tipo de tratamento neurocirúrgico para a dor que envolve lesões na zona dorsal da coluna vertebral, interrompendo a transmissão de estímulos neurais nociceptivos. As principais indicações estão relacionadas às dores oncológicas resistentes à morfina e alguns casos de dor neuropática que atendem aos critérios cirúrgicos.

Objetivo: Realizar revisão da literatura para identificar a eficácia do procedimento DREZ para pacientes com dor neuropática e relatar as consequências desse tipo de tratamento.

Método: Como estratégia de busca, foram utilizados descritores em inglês registrados no Medical Subject Headings (MeSH) e para suporte científico, foram realizadas buscas nas bases de dados PubMed, Medline (BVS) e Science Direct utilizando o operador booleano "OR" para associar os descritores na busca.

Resultado: A lesão da zona de entrada da raiz dorsal (DREZ) ainda é utilizada como opção de tratamento para algumas condições dolorosas, bem como para espasticidade em pacientes selecionados. As técnicas mais comuns para a realização da DREZotomia são a DREZ microcirúrgica e a coagulação por radiofrequência. As dificuldades técnicas no uso de punções para realizar lesões por radiofrequência incluem complicações como lesões na coluna dorsal ou no trato corticoespinhal.

Conclusão: DREZotomia é opção terapêutica eficaz para o alívio da dor neuropática em vários contextos clínicos. No entanto, é importante observar que o alívio da dor pode variar entre diferentes tipos de condições, com taxas de sucesso geralmente mais altas em pacientes com avulsão da raiz nervosa e lesões do plexo braquial.

PALAVRAS-CHAVE: DREZotomia. Cirurgia. Dor neuropática.

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INTRODUCTION

DREZotomy or DREZ surgery is a type of neurosurgical treatment for pain that involves lesions in the dorsal zone of the spine, interrupting the transmission of nociceptive neural stimuli. The main indications are related to oncologic pains resistant to morphine and some cases of neuropathic pain that meet surgical criteria.[1] The most common techniques for its performance are microsurgery and radiofrequency (RF) DREZ coagulation.[2] Microsurgical dorsal rhizotomy is a neurosurgical procedure that selectively cuts muscle and nociceptive fibers, reducing hypertonicity and neuralgic pain.[3] Additionally, ultrasound has been used as an enhancement method for RF DREZ, reducing the risks of complications.[2]

It was initially introduced for pain treatment, especially neuropathic secondary to brachial plexus injury. However, postoperative evaluation showed that, in addition to the analgesic effect, there was a significant decrease in muscle tone and loss of stretch reflexes in the areas corresponding to the operated spinal segments.[3] Therefore, microsurgical excision (DREZ) was attempted in the following years to treat severe spasticity.[3,4] In this context, the causes of brachial plexus-related injuries can be divided into traumatic and non-traumatic. Motor vehicle accidents are the most common cause of brachial plexus injury, followed by birth trauma, sports-related injuries, stabbings, and gunshot wounds. Non-traumatic causes include tumor infiltration, radiation-related injuries, and sometimes congenital factors (cervical ribs). Other less common causes include those related to patient positioning during neurosurgery and orthopedic surgery involving the shoulder joint.[5]

Some inclusion criteria for DREZotomy reported in the literature include persistent neuropathic pain, visual analog scale greater than 5, sleep problems, and the use of high doses of opioids and anticonvulsants for more than 1 year. Additionally, failure of autonomic blockade and neurostimulation points to dorsal root zone ablation as an alternative.[6] It is more effective and safer when indicated to treat large areas of afferent loss, such as brachial plexus root dissection, actinic plexopathy, segmental pain in paralyzed patients with myelopathy or lesions of the cauda equina and medullary cone.[7,8] Other reasons for indication reported in the literature include phantom limb pain, spinal cord injury, and post-herpetic neuralgia.[9] In cases of brachial plexus avulsion, most patients also present with brachial neuralgia, in addition to persistent neurological deficits. About a quarter of these patients suffer from chronic neuropathic pain, often resistant to drug treatment, severely limiting their quality of life.[5]

In cases of nerve root rupture, DREZ surgery shows immediate good and excellent results, observed in majority of patients, fair in a smaller fraction, and unsatisfactory in an even smaller fraction.[5,7,10] During follow-up periods of 5 to 108 months, the rate of good and excellent results generally decreases slightly, and the rate of fair results often increases insignificantly.[7] The literature also reports a significant decrease in neuropathic pain with the use of this procedure around 6 months.[11,12] Over time, partial or complete recurrence of pain commonly occurs in 50% of patients at 6 months, 38% at 1 year, and 26% at 18 months.[7] Motor impairment, usually mild, occurs in approximately 10% of patients with Lissauer's line and posterior spinal horn injuries. In cancer patients, more invasive procedures to properly control pain, including neuropathic pain, should not be delayed because achieving this control will result in a significant improvement in their quality of life, especially in patients with advanced disease and poor prognosis.[7] Furthermore, the literature reports the use of DREZotomy combined with other techniques as an alternative for medullary syringomyelia, showing good results.[13] However, the procedure does not yield satisfactory results in painful syndromes associated with multiple sclerosis.[7]

The reason for performing DREZotomy is to block nociceptive input, preferably in the lateral part of the dorsal root entry zone.[6] In cases of pain with complete deafferentation, such as in brachial plexus avulsion, the goal is to destroy hyperactive nociceptive neurons deep in the tip of the dorsal horn.[14] It´s application for pain related to brachial plexus injury has a significantly higher success rate than other conditions.[2] In these types of procedures, approximately 2/3 of patients use this technique with good long-term results. DREZ has been well studied and described in the literature for treating post-brachial plexus injury neuralgia using various techniques.[5] However, the literature reports some intraoperative morbidities, including cerebrospinal fluid leakage, subcutaneous hematoma, and bacteremia.[4] In this light, surgical intervention remains useful in a significant number of cases that do not respond to drug therapy, both due to a lack of analgesic response and unpopular side effects among patients. Improved knowledge of painful syndromes, the development of new and enhanced existing techniques, and improvements in indications have significantly contributed to increasing the appropriateness and effectiveness of surgical interventions.[7]

In light these considerations, the importance of this topic is evident in the medical literature. So, the present work aims to conduct a literature review to identify the effectiveness of DREZ surgery for patients with neuropathic pain and to report the consequences of this type of treatment.

METHOD

Initially, the theme "Applications of DREZotomy and its surgical applicability" was established. Subsequently, the guiding question: "What are the applications of DREZotomy and the importance of its use for the control of neuropathic pain?" was defined. As a search strategy, English descriptors registered in the Medical Subject Headings (MeSH) were used: "Anesthetic blocks; neurolytic blocks; neuropathic

pain; DREZotomy; deep brain stimulation; cortical electric stimulation; spinal cord electric stimulation; neurosurgery for neuropathic pain; and invasive neuromodulation." For scientific support, searches were conducted on the PubMed, Medline (BVS), and Science Direct databases using the Boolean operator "OR" to associate the descriptors in the search. Search results were selected based on inclusion and exclusion criteria applied to articles available in full. Only original studies related to the theme that addressed the guiding question, in English or Spanish, were included. Duplicate articles, review articles, and those that did not fit the theme of this review were excluded.

RESULT

In Table 1, the selected articles are observed according to authorship, year of publication, journal, language, and object of study. Table 2 demonstrates the description of the objective and results of the sample studies according to authorship.

DISCUSSION

The lesion of the DREZ is still used as a treatment option for some painful conditions, as well as for spasticity in selected patients. Most commonly used techniques for it are microsurgical and RF coagulation DREZ. Technical difficulties in using punctures to perform RF lesions include complications such as injuries to the dorsal columns or the corticospinal tract.

How DREZotomy assists and interferes with neuropathic pain?

Numerous studies have concluded that DREZotomy is an effective and safe method for treating patients with chronic neuropathic pain, especially in cases involving brachial plexus lesions. A study that included 27 patients, where the main causes of pain were brachial plexus lesions (55.6%), followed by neoplasms (18.5%), and 63% of them had already undergone neurostimulation therapy for pain control, observed a reduction in pain, measured through the visual analog scale, of ≥ 50% in 77.8% of patients postoperatively. Moreover, they noted a higher success rate, especially in patients with pain related to brachial plexus lesions (93%), compared to other diseases (41.7%). Over a 22-week period, 59.3% of the patients maintained pain improvement.[15] A cohort of 47 patients undergoing DREZotomy after brachial plexus lesions, with a follow-

TABLE 1 — Metadata of included articles

Authorship	Year	Journal	Language	Object of Study
Fontaine et al.1	2015	Neurochirurgie	French	Neurosurgical treatment of chronic pain
De Monaco, Lopes e Teixeira2	2019	Stereotactic and Functional Neurosurgery	English	Ultrasound-guided DREZotomy – technical note
Goyal et al.3	2021	World Neurosurgery	English	Microsurgical DREZotomy for spastic cerebral palsy
Sindou e Mertens4	2004	Operative Techniques in Neurosurgery	English	DREZ surgery for spasticity in adults
Doddamani et al.5	2021	Clinical Neurology and Neurosurgery	English	Microscissor DREZotomy for post-brachial plexus avulsion neuralgia
Marques, Cavalcante e Pimenta6	2020	Neurosurgical Focus: Video	English	Association of spinal cord stimulation and DREZotomy for complex pain
de Oliveira Júnior et al.7	2016	Revista Dor	Portuguese	Invasive treatments for neuropathic pain
Sindou, Mertens e Wael8	2001	Pain	English	Long-term results of microsurgical DREZotomy for spinal cord/cauda equina injury pain
Mongardi L et al.9	2021	Clinical Neurology and Neurosurgery	English	Systematic review on DREZotomy for intractable pain
Duraffourg, Brinzeu e Sindou.10	2021	Operative Neurosurgery	English	How to do microsurgical DREZotomy for brachial plexus injury pain
Baruah et al.11	2021	British Journal of Neurosurgery	English	DREZotomy for post-brachial plexus avulsion pain – fMRI correlates
Baruah et al.12	2014	Indian Journal of Neurotrauma	English	Preliminary results of DREZotomy for brachial plexus injury pain
Shu et al.13	2016	British Journal of Neurosurgery	English	Spinal cord stimulation + microsurgical DREZotomy for syringomyelia pain
Dauleac et al.14	2021	World Neurosurgery	English	Microsurgical DREZotomy for brachial plexus avulsion pain
Afonso et al.15	2021	Neurocirugia	English	Review of results and predictive factors for DREZotomy success

TABLE 2 — Description of the objective and results of included references according to authorship

Authorship	Objective	Main Results
Fontaine et al.1	To discuss neurosurgical techniques for chronic pain.	Overview of techniques including DREZotomy, highlighting indications and outcomes.
De Monaco, Lopes e Teixeira2	To describe the ultrasound-guided DREZotomy technique.	The approach was feasible and allowed accurate lesion placement.
Goyal et al.3	To evaluate microsurgical DREZotomy in spastic cerebral palsy.	DREZotomy reduced spasticity as an alternative to baclofen pumps.
Sindou e Mertens4	To describe DREZ surgery for adult spasticity.	Provided a step-by-step description and outcomes showing efficacy.
Doddamani et al.5	To report experience with microscissor DREZotomy for neuralgia post-brachial plexus avulsion.	Demonstrated significant pain relief in treated patients.
Marques, Cavalcante e Pimenta6	To report combined spinal cord stimulation and DREZotomy for refractory pain.	The combined approach was effective for complex pain control.
de Oliveira Júnior et al.7	To review invasive treatments for neuropathic pain.	DREZotomy highlighted as a valuable option in refractory cases.
Sindou, Mertens e Wael8	To evaluate long-term outcomes of DREZotomy for spinal cord/cauda equina injuries.	Long-term follow-up showed durable pain relief in most patients.
Mongardi L et al.9	To systematically review long-term results of DREZotomy.	Analysis of 1242 cases confirmed its efficacy for intractable pain.
Duraffourg, Brinzeu e Sindou.10	To provide a video description of microsurgical DREZotomy.	The video demonstrated key steps of the surgical technique.
Baruah et al.11	To assess DREZotomy outcomes and fMRI correlates.	Significant pain relief with associated functional MRI changes.
Baruah et al.12	To present preliminary results of DREZotomy for brachial plexus injury pain.	Early results showed efficacy in neuropathic pain reduction.
Shu et al.13	To report spinal cord stimulation combined with DREZotomy for syringomyelia pain.	The combined approach led to satisfactory pain control.
Dauleac et al.14	To present microsurgical DREZotomy results for brachial plexus avulsion pain.	Confirmed efficacy and described surgical nuances.
Afonso et al.15	To review outcomes and predictive factors for successful DREZotomy.	Identified factors associated with better surgical success rates.

up of 32 months, showed similar results, where 70.4% rated pain relief as excellent, 10.6% as good, 7% as fair, and 12% experienced unsatisfactory pain relief; 87% experienced some pain relief, with 81% of them showing long-term analgesic effects (improvement of > 50% in pain).[5]

The disappearance of neuropathic pain in these patients tends to be immediate after surgery.[6,10,13] A case report of a 63-year-old man with brachial plexus lesions associated with neuropathic pain for 42 years, who underwent DREZotomy, found that the patient described complete disappearance of pain postoperatively, persisting for 1 year of follow-up.[10]

Furthermore, it can be observed that patients with more chronic pain present better results. A prospective study that followed 18 patients undergoing DREZotomy after brachial plexus lesions for 6 months found moderate to good pain control in 58.3%, especially in those with a history of chronic pain for more than 10 years, compared to those with pain duration of less than 6 months.[11]

Postoperative management

Despite being a safe and effective long-term procedure, some studies have reported complications, as is common in any surgery. A literature review, that included 46 articles with 1242 participants, described the most reported complications as severe neurological deficit with limitation of daily activities (1.92%), mild neurological deficit without any limitation (11.51%), and temporary postoperative neurological deficit spontaneously recovered within 8 weeks (6.59%), cerebrospinal fluid fistulas (1.19%), complete or partial loss of sphincters (0.44%), surgical hematoma (0.32%), surgery-related deaths (0.62%), and infections (0.99%). Additionally, they observed that the complication rate was higher in patients undergoing the radiofrequency procedure (34.25%) compared to those with microsurgical procedure (14.58%).[9]

It is also common for patients to report postoperative hypoesthesia in the dermatomes corresponding to DREZ lesions.[2,5,9,13] A prospective clinical study that included 7 patients with spastic cerebral palsy, with an average age of 12.[2] years, reported that immediately after surgery, all patients reported varying degrees of sensory loss in the dermatomes of the operated spinal segments, with improvement within 1 to 2 months after surgery. No patients in the study had infection at the wound site, cerebrospinal fluid fistula, or operative mortality.[3] A cohort of 27 patients observed similar complications, where 4 patients had severe neurological deficits, with complete recovery during the follow-up period, but 2 (7.4%) had permanent deficits.[15]

Moreover, patients commonly develop so-called mirror pain, caused by contralateral changes in normal neuronal function after peripheral nerve injury. A case report of a 52-year-old patient, involved in a car accident 30 years ago, initiated mirror pain symptoms in the first week postoperatively.[6]

Regarding the pharmacological control of pain postoperatively, some studies report that the procedure helps reduce the use of chronic pain medications.[2,12,15] The aforementioned cohort of 27 patients found a reduction in routine analgesic treatment in 70.4% of study participants.[15] Another study with 7 patients demonstrated comparable results, where 3 needed minimal or no analgesics after surgery.[8]

Radiotherapy and DREZotomy

The most commonly used DREZotomy techniques are microsurgical and RF coagulation. However, aiming to minimize the risk of complications, a study described an RF technique associated with intraoperative ultrasound, allowing the surgeon to differentiate between gray and white matter, showing the correct entry zone, the angle of introduction of the RF electrode, and the depth, and presented good results in the reported case, where no complications occurred during the procedure.[2]

CONCLUSION

This procedure involves the controlled lesion of the dorsal zone of the spinal cord, interrupting the transmission of nociceptive neural stimuli. Two main techniques are used to perform DREZotomy: microsurgery and radiofrequency coagulation DREZ. Besides pain relief, other indications include phantom limb pain, spinal cord injury, and post-herpetic neuralgia. However, DREZotomy does not appear to be effective for painful syndromes associated with multiple sclerosis. It is important to note that pain relief can vary among different types of conditions, with generally higher success rates in patients with nerve root avulsion and brachial plexus injuries. Nevertheless, DREZotomy is not without risks. Complications seem to be relatively rare, and the surgical intervention remains a valuable option in cases where drug therapy is not effective or causes unwanted side effects. Additionally, there are side effects, such as a reduction in muscle tone and stretch reflexes in areas associated with the operated spinal segments. Consequently, the technique has started to be used in the treatment of severe spasticity. Although it presents potential complications, its benefits in reducing chronic pain and improving the quality of life are evident.

Author´s contribution

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Understanding the origin of paraganglioma

Compreendendo a origem dos paragangliomas

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ABSTRACT

Introduction: Paragangliomas are rare, slow-growing neuroendocrine tumors, often grouped with pheochromocytomas due to their cellular similarities. They arise from neural crest cells and can be found within the sympathetic or parasympathetic nervous systems, with varied clinical presentations, depending on their location and functionality.

Objective: To prepare a comprehensive review of paragangliomas in the context of neurosurgery.

Method: The review used the PubMed, Scopus and Web of Science databases. Studies on epidemiology, pathophysiology, genetic characteristics and clinical manifestations were included. Inclusion criteria included clinical studies, systematic reviews and case studies published between 2000 and 2023. The analysis focused on the neurosurgical aspects of treatment, associated risks and advances in the diagnosis and management of these neoplasms.

Result: 68 articles that focused on the topic referred to in this review were included.

Conclusion: Although they are predominantly benign, approximately 10% present malignant behavior. Its highly vascularized nature and proximity to critical neurovascular structures present surgical challenges. Genetic testing, especially for SDH gene mutations, plays an important role in directing management and assessing the risk of malignancy.

KEYWORDS: Paragangliomas. Pheochromocytomas. SDH mutations. Neuroendocrine tumors. Genetic syndromes. Neurosurgery. Familial syndromes. Head and neck tumors.

RESUMO

Introdução: Os paragangliomas são tumores neuroendócrinos raros e de crescimento lento, frequentemente agrupados com os feocromocitomas devido às suas semelhanças celulares. Eles surgem a partir de células da crista neural e podem ser encontrados dentro dos sistemas nervosos simpático ou parassimpático, com apresentações clínicas variadas, dependendo da sua localização e funcionalidade.

Objetivo: Elaborar ampla revisão sobre paragangliomas no contexto da neurocirurgia.

Método: A revisão utilizou as bases PubMed, Scopus e Web of Science. Foram incluídos estudos sobre epidemiologia, fisiopatologia, características genéticas e manifestações clínicas. Os critérios de inclusão abrangeram estudos clínicos, revisões sistemáticas e estudos de caso publicados entre 2000 e 2023. A análise foi focada nos aspectos neurocirúrgicos do tratamento, riscos associados e os avanços no diagnóstico e manejo dessas neoplasias.

Resultado: Foram incluídos 68 artigos que focaram o tema referido nesta revisão.

Conclusão: Apesar de serem predominantemente benignos, aproximadamente 10% apresentam comportamento maligno. Sua natureza altamente vascularizada e a proximidade com estruturas neurovasculares críticas apresentam desafios cirúrgicos. O teste genético, especialmente para mutações no gene SDH, desempenha papel importante para o direcionamento do manejo e na avaliação do risco de malignidade.

PALAVRAS-CHAVE: Paragangliomas. Feocromocitomas. Mutações SDH. Tumores neuroendócrinos. Síndromes genéticas. Neurocirurgia. Síndromes familiares. Tumores de cabeça e pescoço.

Central Message

The article addresses paragangliomas, rare neuroendocrine tumors that share characteristics with pheochromocytomas, focusing on their particularities, epidemiology, pathophysiology, genetic analysis and clinical presentation. By exploring molecular and genetic characteristics, the article reveals the importance of differentiating between sporadic and hereditary forms, highlighting specific mutations such as those of the SDH enzyme complex. In addition, it emphasizes the surgical challenges and the classification of these tumors as "ongoing risk" due to their indeterminate behavior.

Perspective

A comprehensive review of paragangliomas in the context of neurosurgery is important, and offers detailed analysis of their biological characteristics, relevance of genetic variants, and their influence on clinical presentation and management. The article also highlights the importance of multidisciplinary approach, including genetic screening for those diagnosed with paraganglioma, especially with mutations associated with higher risk of malignancy or aggressive behavior.

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INTRODUCTION

Paragangliomas are rare, slow-growing neuroendocrine tumors. They show little difference with pheochromocytomas, being indistinguishable at the cellular level. It is noteworthy that when it comes to nomenclature, in 2004 the World Health Organization referred to paragangliomas as "extra-adrenal pheochromocytoma", currently the distinction aims to more accurately catalog associated neoplasms, risk of malignancy and genetic tests. Thus, paragangliomas can be defined as neuroendocrine tumors of the extra-adrenal autonomic paraganglia. As a rule, they are derived from embryonic neural crest cells.[1-2]

The presentation of a paraganglioma can be in the sympathetic or parasympathetic nervous system. The former are usually catecholamine secretors, influencing blood pressure autoregulation, manifesting with hypertension, headache, and tachycardia. They are located in paravertebral ganglia of the chest, abdomen and pelvis. In turn, the latter, for the most part, are non-functional and are along the glossopharyngeal and vagal nerves, with a higher incidence in the neck and skull base.[2]

Commonly, due to its slow growth and characteristic histology, it has a typically benign behavior; however, about 10% evolve with clinical characteristics of malignancy; for this reason, they are currently classified as tumors of continuous risk. In addition, being highly vascularized and depending on the implantation site along the vascular-nervous bundle, they represent a surgical challenge when indicated.[3-4] Thus, this article aims to develop a broad review of paragangliomas in the context of neurosurgery.

METHOD

This study used PubMed, Scopus, and Web of Science as the search base. Publications on the epidemiology, pathophysiology, genetic characteristics and clinical manifestations of paragangliomas were included. Inclusion criteria covered clinical studies, systematic reviews, and case studies published between 2000 and 2023. The analysis focused on the neurosurgical aspects of treatment, associated risks, and advances in the diagnosis and management of these neoplasms. Only articles that contained the theme referred to in this review were included.

DISCUSSION

The incidence of paragangliomas is often described together with that of pheochromocytomas due to their common characteristics. Thus, it is still difficult to characterize the specific incidence of paragangliomas. However, it is worth noting that studies agree on their rarity, citing that they correspond to approximately 0.6% of head and neck neoplasms, as well as an incidence of 0.[8] per [100,000] person-years.[1-4]

Paragangliomas were considered for many years to be sporadic; However, more and more studies show the discovery of genetic tendencies with tumors of their own characteristic. To expose this fact, some epidemiological characteristics of sporadic tumors can be highlighted, such as their appearance in middle-aged patients - 40 to 50 years - and a prevalence of 71% in females; A reason for such a presentation is not yet well described. At this point, it can be seen that although they are still considered mostly sporadic, there are recent data on genetic tendencies linked to paragangliomas and hereditary syndromes, where patients with genetic load tend to develop them earlier, up to 10 years before the usual age. In addition,- the prevalence between men and women becomes indifferent.[1-5]

The genetic load has shown increasing significance, with the SDH protein mutation being the most described. Hereditary/familial syndromes have also been reported, with a greater influence on head and neck paragangliomas, representing up to 40% of cases, as well as being one of the reasons for their appearance in children.

Pathophysiology

Paragangliomas originate from cells derived from the neural crest, thus involved in the pluripotentiality, migratory and proliferative capacity of these cells. Thus, although they have been considered benign for many years, the WHO has recently characterized them as tumors of continuous risk, since there is no histological classification system for them, as they are considered to have indeterminate biological potential.[6]

The disparity observed in sporadic paragangliomas vs. paragangliomas with genetic trait is reinforced. It is noted that the first carotid in the body were observed more frequently in individuals exposed to chronic hypoxia, being related to patients who inhabit high altitudes with significantly thinner air, as well as patients with cyanotic congenital heart disease and chronic obstructive pulmonary disease.

Hypoxia factor is also reported in the presence of malignancy of paragangliomas and pheochromocytomas. It is theorized that with hypoxia, enzyme losses occur, leading to the accumulation of metabolites, directly inducing malignant phenotypes.[7] Some reported mechanisms cite the physiology of increased red blood cell production, which has already been well described, highlighting the hypoxia-induced binding of factor 1 (HIF1) and vascular endothelial growth factor (VEGF). The first, considered to regulate the expression of hundreds of genes, encompasses those that encode metabolic enzymes, angiogenic factors and cell cycle regulators.[7-9] In addition, a HIF stabilizer has already been described and approved in the treatment of anemia. In addition, HIF2 inhibitors have been developed with promising results in kidney cancers, also considered pseudo-hypoxic tumors.[10,11]

Regarding possible genetic origins, there is a considerable range of studies on molecular variants corresponding to paragangliomas. Before entering into the subdivisions of hereditary syndromes and possible molecular alterations with subsequent origin of paragangliomas, it should be noted that, although studies have considered data together with

pheochromocytomas, recent studies have shown that most paragangliomas in children under 18 years of age have genetic traits, reaching 56% of those affected. On the other hand, when focusing on those found in children under 5 years of age, this percentage increases, reaching 70-85%.[12-14] It is also important to highlight that when compared to adults, pediatric paragangliomas present more like multiple paragangliomas.[12,15]

Even though most paragangliomas continue with sporadic diagnosis, it should be noted that with modern genetic tests a wide range of enzymatic alterations and hereditary syndromes are described as risk factors for their development, described together with pheochromocytomas, as explained in the introduction. Among the alterations, genes encoding some subunits of the enzyme complex, succinate dehydrogenase (SDH), as well as 4 syndromes described, namely, multiple endocrine neoplasia, types 2A and 2B (MEN2); neurofibromatosis type 1 (NF1); von Hippel Lindau disease (VHL) and the Carney-Stratakis dyad, with the pathogenic variants SDHD, SDHB and SDHC, VHL and NF1 explaining most familial paragangliomas.[16]

Although with great pathogenic variability, genetic traits are described in studies with genetic screening, again emphasizing alteration of the SDH subunit, being SDH-D in 9.3%, SDH-B in 4.8%, SDH-C 0.8%, in addition to 2.2% of NF1.[7] It is noteworthy for this article that all 15 patients who presented skull and neck base paragangliomas or secretory paragangliomas also had a pathogenic variant of the germline. These data are similar to published genetic screenings, where 30% of patients with pheochromocytoma/paraganglioma had familial syndrome or susceptibility gene, with VHL in 9%, SDHD in 7.1%, SDHB in 5.5%, RET in 5.3% and NF1 in 2.9%.[7]

As mentioned above, most studies do not differentiate pheochromocytomas from paragangliomas due to their similarity at the cellular level However, when separated by a study with genetic screening, a significant difference was observed in terms of presentation, where pathogenic variants were found in 83% of those with paragangliomas, in contrast to 57% of those with pheochromocytoma.[8,9] Patients with multiple tumors also stand out -20% of 24.83%.[17]

Genetic analysis of SDH factor

Among the variants of the SDH enzyme complex, paraganglioma syndromes 1, 2, 3, 4 and 5 (PGL1, PGL2, PGL3, PGL4 and PGL5, respectively) stand out with greater precision. According to the error in the subunit, one can identify individual characteristics of the syndromes that follow.[1]

PGL1

It is associated with the SDHD variant at the 11q23 genetic locus, being the most common type of familial syndromes. In addition, SDHD is a gene with a putative maternal imprint, that is, it is limited to paternal genetic inheritance. It should be remembered here that paternal pathogenic variants are considered highly penetrating in middle age, reaching 50% precisely in the period of prevalence of paragangliomas.[7,10,11]

When it comes to head and neck paragangliomas, interesting data emerge from the 236 patients in a Dutch study, where, of all patients, up to 83% were carriers of a pathogenic variant SDHD, and a single founding pathogenic variant, p.Asp92Tyr, accounted for 72% of skull base and neck paragangliomas.[16] Another study in Sweden shows that in the face of phenotype we have both paragangliomas and pheochromocytomas; however, paragangliomas accounted for up to 93%.[7] In addition, it is observed that paragangliomas were mostly parasympathetic, up to 84%, and many of them multiple, up to 56%, although rarely malignant 4%.

PGL2

It is associated with the SDH2 complex assembly variant at the genetic locus 11q12.[2,] reported only in 2 European families, with only parasympathetic paragangliomas being observed, being multiple in its majority.[7,17,18]

PGL3

It is associated with the SDHC variant in the locus genetic 1q21. It demonstrates rarity and predominance in parasympathetic paragangliomas.

PGL4

It is associated with the SDHB variant at the genetic locus 1p36.1-35, being the second most common type of familial paraganglioma. Genetic modifications of SDHB are also reported with renal cell carcinoma. The phenotype also includes pheochromocytomas; however, the majority, up to 78%, corresponds to paragangliomas, of which the majority of the sympathetic system is multiple. Penetrance usually represents 25% at 50 years of age, and 10% of those investigated demonstrated a family history. When talking about mutations related to SDHB, the secretion of catecholamines, including norepinephrine and some cases dopamine, is a typical characteristic. Some important features about SDHB-related paragangliomas are that these tumors appear earlier, around age 28, and dopamine secretion is related to a worse prognosis; variants of SDHB have a higher rate of malignancy. Thus, when there is a diagnosis of paraganglioma with variant of SDHB, the investigation of metastatic disease is indicated.[10,19-22]

PGL5

It is associated with the SDHA variant, with 3 nonsense pathogenic variants reported (p.Arg585Trp, p.Arg589Trp, and p.Arg31X). The mean age was 40 years, and the phenotype varies between pheochromocytoma and paraganglioma. Finally, variants were found in healthy control patients, inferring low penetrance in patients with SDHA.[23,24] Considering the data on germline variants of the SDH above, genetic screening is recommended in all patients diagnosed with paraganglioma.

Analysis of other genetic alterations

In addition to PGL due to SDH variations, some

hereditary syndromes that course with the paraganglioma or pheochromocytoma phenotype are: MEN2, NF1, VHL and the Carney-Stratakis dyad. Recently, the MAX protein variant was also discovered.

MEN2

Paragangliomas are rarely observed, being more related to pheochromocytomas, including bilateral ones. It can also be subdivided into MEN2A and MEN2B according to the variant of the RET proto-oncogene. MEN2A is characterized by medullary thyroid cancer, pheochromocytoma/paraganglioma, and primary parathyroid hyperplasia. MEN2B is characterized by medullary thyroid cancer, pheochromocytoma/paraganglioma, but without hyperparathyroidism.[7]

NF1

NF1 is a tumor suppressor gene on chromosome 17q11.1 that characterizes neurofibromatosis type 1, with a range of clinical findings including pheochromocytomas/paragangliomas. It is important to report that pathogenic variants of NF1 are often acquired and not inherited, generating a mosaic phenotype. As a rule, paragangliomas are rare in this alteration and, when present are located in periadrenal areas.[7,25]

VHL

The VHL gene is a tumor suppressor gene on chromosome 3p25-26, its products regulate hypoxia-inducible factor (HIF) oxygen dependence. Between 10-34% of von Hippel-Lindau patients develop pheochromocytoma/noradrenergic paraganglioma.[7,17] The risk of developing the tumor is higher in families with type 2 disease than type 1; in addition, it should be noted that in the families of VHL type 2, pathogenic variants Y112H were diagnosed in the elderly, and the tumors were more likely to secrete vanillmandelic acid (VMA), and less likely to secrete norepinephrine. In addition to being more multifocal, they had lower rates of surgical cure (76% vs. 100%), as well as a higher rate of malignancy (20% vs. 5%) and a worse prognosis.[26]

Dyad Carney – Stratakis

An autosomal dominant disease with incomplete penetrance27, it is of primary significance because it characterizes gastrointestinal stromal tumors (GISTs) and paragangliomas, often attributed to the germline pathogenic variant of SDHB, SDHC, or SDHD.[28,29]

MAX

It is a gene located on chromosome 14q23.[3.] Some patients with pheochromocytoma/paraganglioma without other pathogenic variants have been identified with germline pathogenic variants in MAX.[30]

Presentations

Although the phenotype encompasses pheochromocytoma and paraganglioma, regarding paragangliomas, and their presentations, some peculiarities can be mentioned with some classifications as follows: sympathetic or parasympathetic, solitary or multiple, sporadic or hereditary, benign or malignant.

Paralymph node paragangliomas are usually located along the glossopharyngeal and vagus nerves, with a higher incidence in the neck and skull base. Up to 60% of carotid body tumors are in the neck and skull base. In these cases, most are non-functional, presenting symptoms usually due to the mass effect.[31]

Sympathetic paragangliomas are located along the sympathetic chain from the base of the skull to the bladder and prostate. Most are functional with hypersecretion of catecholamines. Up to 75% of tumors appear in the abdomen, with a predilection for the junction of the vena cava with the left renal vein, or in the aortic bifurcation. Up to 10% of tumors appear in the chest. They can also arise in the thyroid, adjacent to the thoracic spine, and in the cauda equina. 32-37

Approximately 26% of paragangliomas are thought to be multiple and 1/3 are associated with hereditary syndrome, as mentioned above. Also, it is observed that 15-20% of tumors with hypersecretion are extra-adrenal. Finally, multiple tumors appear to be much more frequent in hereditary cases than sporadic ones: 17% to 85% vs. 1.2%.[38]

Malignancy is seen in 20% of extra-adrenal secretory paragangliomas. When found at the base of the skull and neck, they are usually benign. As mentioned in PGL4, SDHB variants are usually malignant and have a worse prognosis. 39-41

The findings usually correspond to one of the following cases: mass effect, hypersecretion of catecholamines, incidental asymptomatic or asymptomatic in a carrier of a pathogenic variant.[1,31,42]

Diagnosis

Due to their catecholamine-secreting characteristic, all paragangliomas should be tested for hypersecretion in 24-h urine or serum collection, even in those without clinical suspicion. That said, the diagnosis of secretory paraganglioma is made through measurements of urinary or plasma fractionated metanephrines and catecholamines.

Secretors

In general, there is still no consensus in the literature on the best test for diagnosing paraganglioma. As a rule, except for MEN2-related tumors that secrete epinephrine, most tumors are norepinephrine-secreting.

For tumor location, the biochemical test should be followed by radiological evaluation, CT or MRI, investigating according to the predilection of the tumor location mentioned in "presentation". It should be noted that MRI can distinguish paragangliomas from other masses, and CT misses up to 1/4 of the tumors related to MEN2 syndrome. After these processes, a cross-sectional image of the thorax/head and neck is justified in the face of previous images with negative results. It is followed with radioisotope imaging if it remains negative. It is noteworthy that radioisotope imaging is also justified as a screening for metastatic disease in patients with high probabilities of malignant tumors.

Conventional PET imaging is considered to have a high degree of sensitivity, being an interesting choice both in primary tumors and in metastases.[43,44] With the emergence of somatostatin analogues and positron-emitting radiomarkers, it is possible to combine with CT-integrated PET; 2 examples are gallium Ga-68 DOTATATE and gallium Ga-68 DOTATOC, which can improve the detection and staging of neuroendocrine tumors, including paraganglioma.[45-47]

It should be noted that for surgical planning, or even clinical decision, fine-needle biopsy is contraindicated for any type of catecholamine-secreting tumor; therefore, it is contraindicated for the vast majority of paragangliomas.[48]

Non-secretors

Of the paragangliomas that course with mass effect, the following cases will be highlighted:

1) Tumors of the carotid body: As a rule, they are painless masses, with a rubbery appearance, being more mobile horizontally than vertically, characterizing Fontaine's sign. They show a gradual increase. It can also present as a pulsatile mass and with carotid murmur. They displace the posterolateral common carotid bifurcation of the internal carotid.[49]

2) Julgulotimpanic paragangliomas: Also slow-growing, they culminate in conductive hearing loss, or pulsatile tinnitus. In addition, there may be deficits of the lower cranial nerves, with greater impairment of the easy nerve. Also, during the physical examination, a bluish pulsating mass may be visible behind the tympanic membrane.[49]

3) Vagal paragangliomas: It can occur at any point of the cervical vagus nerve, usually appear in the inferior nodosum ganglion. They displace the internal and external carotid artery anteriorly and cause erosion and enlargement of the jugular foramen. Thus, there can be several symptoms, including facial drooping, cranial nerve deficits or even Horner's syndrome.[50]

It is worth remembering that paragangliomas in the dura mater can course with neurological compression.

Considering diagnostic tests, ultrasonography or cross-sectional CT or MRI images are included in the initial evaluation of skull base and neck paragangliomas. In a carotid body tumor, US demonstrates a solid, well-defined, hypoechoic tumor with enlargement of the carotid bifurcation.[51,52]

On CT, the classic findings of paraganglioma demonstrate a homogeneous mass with non-contrast-enhanced Hounsfield units in the range of 40 to 50, in addition to cystic changes, necrosis, and internal calcifications in many cases.[1] That said, CT is the best initial imaging test when julgulotimpanic paraganglioma is suspected, due to its better method of evaluating the destruction of the temporal bone in its extension. It contributes to the Fisch classification at the stage, although the studies do not present consensus on staging systems, they are important in the choice of surgical approach.

Regarding the use of contrast, it should be noted that all patients must have a negative biochemical result for hypersecretion of catecholamines or undergo alpha blockade before receiving ionic contrast, in order to avoid catecholamine crisis. The use of nonionic contrast is considered safe.[53,54]

Regarding gadolinium MRI, it provides a greater definition of the relationship between paragangliomas and adjacent vascular structures, and is recommended in some guidelines.[55] It is considered complementary to CT in julgulotalamic patients, with the objective of detecting dural infiltration and intradural tumor growth. In addition, it is also the test of choice in children and pregnant women or in those allergic to CT contrast.

Paragangliomas in children

Considering the limitation of experiments and studies on paragangliomas in children, the data are mixed with the adult literature. However, it is feasible to discuss this topic with some recent data.

Again, the cellular similarity between the paraganglioma and pheochromocytoma phenotypes is mentioned, which, when considered together, represent 0.^{3} cases per million per year, with approximately 20% of these diagnoses in childhood. When the research in hypertensive children is isolated, the incidence varies from 0.^{8} to 1.7%. Another worrying fact occurs when compared to adults; smaller patients are more likely to have malignant and multicentric tumors, in addition to greater link with genetic factors. Even if up to 2/3 have no family history of disease, up to 56% have germline pathogenic variants of the genesRET, VHL, SDHD, SDHB, SDHC, SDHAF2 or SDHA, as well as TMEM127 or MAX.

Regarding malignancy, a causal factor is not yet well established. However, 2 studies reported that almost 50% of the children had malignant/metastatic disease[56,57], compared to approximately 30% in adults.[56,57] The increased rate of malignancy among children was debated in one study, being explained by their higher rate of pathogenic cluster 1 variants, especially SDHB and VHL.[57]

CONCLUSION

Paragangliomas have a complex combination of genetic and environmental factors that influence their presentation and prognosis. Early identification of genetic mutations can guide clinical management, especially in cases with a higher risk of malignancy. Advances in the understanding of pathophysiology, including the role of HIF, may result in new therapeutic approaches. In the neurosurgical context, adequate planning for the resection of highly vascularized tumors remains a challenge, reinforcing the importance of a multidisciplinary approach.

Authors' contributions

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Viviane Aline Buffon: Conceptualization, Investigação
Milton Manrique Rastelli Junior: Data curation, Writing – original draft
Giovana Nascimento Antocheviez: Conceptualization, Investigação
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BioSCIENCE Review Article
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Current advances and challenges in the use of polymethylmethacrylate (PMMA) bone cements in neurosurgery

Avanços e desafios atuais sobre o uso de cimentos ósseos de polimetilmetacrilato (PMMA) na neurocirurgia

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ABSTRACT

Introduction: Cranioplasty is essential for cranial reconstruction after craniectomy, using autologous grafts (gold standard) or synthetic materials. PMMA stands out for its economic feasibility and intraoperative flexibility, despite a high complication rate.

Objective: Provide comprehensive analysis of the evolution of PMMA and its variants, highlighting its advances, challenges and continued need for innovations.

Method: An integrative review of 32 recent studies on PMMA in cranioplasty was conducted, selecting articles from PubMed, MedLine, and ScienceDirect. Included sources comprised original articles, reviews, and computational studies from the last 10 years. The search used descriptors such as "Polymethyl Methacrylate" AND "Cranioplasty."

Result: PMMA is widely used and can be intraoperatively shaped, but it presents a high risk of complications. Alternatives include antibiotic-impregnated PMMA, which reduces infections, and customized 3D implants, which optimize aesthetics and surgical time despite higher costs.

Conclusion: Cranioplasty with PMMA is accessible and versatile but has a high complication rate. Strategies such as antibiotic impregnation and improved techniques help mitigate risks. 3D biomaterials emerge as a promising alternative, though more expensive. The choice should balance cost, safety, and patient needs.

KEYWORDS: Cranioplasty. PMMA. Bone cement. Synthetic materials. Polymers.

RESUMO

Introdução: A cranioplastia é essencial para reconstrução craniana após craniectomia, utilizando enxertos autólogos (padrão-ouro) ou sintéticos. PMMA destaca-se pela viabilidade econômica e flexibilidade intraoperatória, apesar da alta taxa de complicações.

Objetivo: Oferecer análise abrangente da evolução do PMMA e suas variantes, destacando seus avanços desafios e necessidade contínua de inovações.

Método: Foi realizada revisão integrativa de 32 estudos recentes sobre PMMA em cranioplastias, selecionados nas bases PubMed, MedLine e ScienceDirect. Foram incluídos artigos originais, revisões e estudos computacionais dos últimos 10 anos. A busca utilizou descritores como "Polymethyl Methacrylate" AND "Cranioplasty".

Resultado: PMMA, amplamente usado, pode ser moldado intraoperatoriamente, mas apresenta risco elevado de complicações. Alternativas incluem PMMA impregnado com antibióticos, reduzindo infecções, e implantes personalizados em 3D, otimizando estética e tempo cirúrgico, apesar de custos elevados.

Conclusão: A cranioplastia com PMMA é acessível e versátil, mas apresenta alta taxa de complicações. Estratégias como impregnação antibiótica e técnicas aprimoradas ajudam a mitigar riscos. Biomateriais 3D surgem como alternativa promissora, embora mais caros. A escolha deve equilibrar custo, segurança e necessidades do paciente.

PALAVRAS-CHAVE: Cranioplastia. PMMA. Cimento ósseo. Materiais sintéticos. Polímeros.

Central Message

Cranioplasty is an essential procedure to restore function and aesthetics after craniectomy, with significant advances in the use of implants. PMMA stands out as a viable alternative, despite the associated complications, and is widely used due to its economic viability and intraoperative flexibility. The introduction of techniques such as 3D printing and the use of PMMA impregnated with antibiotics have demonstrated improvements in the safety and efficacy of cranioplasties. However, challenges such as bone resorption, infection, and high costs of custom implants have yet to be overcome. Thus, this review explores the evolution of PMMA and the prospects for improvement in cranioplasty.

Perspective

The evolution of cranioplasty reflects significant advances in the search for ideal materials, balancing biocompatibility, strength, and affordability. PMMA remains a widely used choice, but its high complication rate drives the search for bioactive alternatives. The development of techniques such as 3D printing and antibiotic impregnation has shown potential to optimize results and reduce risks. However, challenges such as high costs and lack of standardization still limit its widespread application. Future studies should focus on the personalization of implants and strategies that reconcile clinical efficacy and economic viability.

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INTRODUCTION

Cranioplasty is a frequent procedure in neurosurgical patients after craniectomy, with the aim of reconstructing functional and aesthetic sequelae resulting from various conditions. The continuous evolution of implant materials plays a key role in the advancement of surgical practices, especially in reconstructive procedures. In this context, neurosurgeons face complex challenges, such as the precise choice of implants, optimal timing for interventions, management of postoperative complications, and prevention of reoperations, and the best strategy is still the subject of debate.[1,2]

The use of autologous bone grafts - considered the gold standard - offers significant advantages, since these living tissues have important biological properties such as growth potential, resistance to infections, radiotransparency, stability, low thermal conduction and good malleability, in addition to not implying additional costs.[3-6] Feroze et al.[7] present an analysis of the evolution of cranioplasty, highlighting the continuous search for ideal alloplastic material, characterized by the desirable properties of native bone. A comprehensive study of diverse alternatives, such as metals, acrylics, ceramics, and plastics, highlights titanium as a notable choice in contemporary surgical practice. Modern alloys, such as aluminum, have played a crucial role in the development of more affordable and heat-resistant implants. Acrylics, especially methyl methacrylate (MMA), have emerged as economically viable alternatives, although their limited osseointegration capacity imposes restrictions on their application in children. Ceramics, such as hydroxyapatite and CCPC, demonstrated simplified application, while they faced a greater propensity to fractures. Contemporary plastics, such as porous polyethylene and PEEK, emerge as durable options for calvarial repair.[7] In this scenario, the adoption of synthetic alternatives, with a focus on polymethylmethacrylate (PMMA), is often indispensable in circumstances that include severe bone graft resorption, bone fractures, infections, and restrictions at the donor site.[1,8,9] One of the main advantages of PMMA in comparison with other materials, in this sense, lies in its economic viability, flexible intraoperative application with adjustment to individual anatomy, bone window permeability, and its availability in cement form, making it a frequent choice among neurosurgeons.[4,6,8,10-12]

Although PMMA implants have advantageous properties, it is crucial to highlight the high rate of revision and complications in cranioplasty. In addition, the scarcity of prospective multicenter studies on postoperative complications between autologous and synthetic cranioplasty hinders comprehensive analysis, limiting the understanding of the best approaches and materials.[1,6,10,11,13,14]

The introduction of 3D printing techniques in medicine and the manufacture of custom and prefabricated implants has contributed to the improvement of aesthetics and long-term efficacy. Despite the challenges of cost and production time, affordability has been increasing, mainly due to the significant reduction in prices in recent years. In this scenario, several studies seek to develop techniques to mitigate risks and reduce operating costs related to these innovations.[15-18]

On the other hand, the continuous effort to improve biocompatibility highlights growing interest in the development of biomaterials, aiming to optimize biomechanical properties, the bone-cement interface, and reduce bone resorption. The gradual transition of PMMA to bioactive versions, although promising, requires a balanced approach to preserve its essential physical properties.[1,2,19]

In this sense, the present review seeks to provide a comprehensive analysis of the evolution of PMMA and its variants, highlighting its notable advances, challenges, and the continuous need for innovations to improve clinical efficacy in cranioplasty.

METHOD

This research is an integrative review of the literature on recent studies on the use of PMMA in neurosurgical interventions, with a specific focus on cranioplasty, cranial reconstruction and repair of cranial defects through the use of cranial implants. The selection of articles was carried out using strategically chosen Boolean search descriptors and operators, namely: "polymethyl methacrylate" OR "PMMA" OR "acrylic bone cement" OR "methyl methacrylate" AND "neurosurgery" OR "neurosurgical procedures" OR "cranial surgery" AND "cranioplasty" OR "cranial reconstruction" OR "skull defect repair" OR "cranial implants". The search covered the PubMed, MedLine and ScienceDirect databases, considering exclusively studies published in the last 10 years, without language restrictions and available in full. In total, 32 articles were carefully selected to compose this review. The selection criteria were original studies, literature reviews and computational studies, as long as they are related to the topic. At the same time, duplicate articles and those that did not fit the theme of this review were excluded. The choice of this methodology aimed to ensure the inclusion of recent and diverse studies, for broad and up-to-date understanding.

DISCUSSION

Implant materials currently available cover a variety that encompasses autologous grafts and allografts. It is noteworthy that autologous bone grafts stand out for their ability to confer superior resistance to infections and reduced likelihood of extrusion. However, these grafts also face considerable challenges, including variable resorption, difficulties in the remodeling process, and the occurrence of morbidities associated with the donor site. Thus, there is a transition to synthetic alternatives in specific situations, such as severe graft resorption, bone comminution, infection, and limitations related to the donor site.[20,21] PMMA, despite its limitations, stands out as an alternative widely used in clinical practice, being molded intraoperatively to form a plate fixed to the cranial defect through perforations.[13]

The management of surgical complications requires a distinction between intraoperative and postoperative

complications. Risk factors for post-cranioplasty infections include associations with the surgical timing, the location of the cranial defect, surgical site conditions, and the presence of catheters. Complex surgical regions, on the other hand, include previously irradiated tissues, conditions of active infection, cerebrospinal fluid leaks, and the existence of skin lesions or scars resulting from trauma.[1,8,10,22] Worm et al.[10] emphasizes that cranioplasty flap infection often requires removal, resulting in a second surgical intervention and an antibiotic regimen lasting at least 4 weeks, which can result in a significant increase in morbidity and hospital costs.

The use of PMMA impregnated with antibiotics appears as a viable alternative, economically accessible and with the possibility of reducing the risk of infection in cranioplasty, its use has been documented since the 1970s, with erythromycin being a pioneering additive. Currently, aminoglycosides have stood out due to their reduced allergic profile and broad-spectrum antimicrobial activity.[2,10] In a prospective, longitudinal and uncontrolled study10 in a tertiary hospital of high complexity in Brazil, the use of PMMA impregnated with antibiotics in moderate and large cranial defects was evaluated. The results revealed a low incidence of postoperative infectious complications, indicating its efficacy in reducing morbidity, mortality, and hospital costs. The authors also highlighted that the infection rate observed in patients undergoing cranioplasty with antibiotic-impregnated PMMA was significantly lower than the data described in the literature.[10] Clinical variability in this scenario is associated with factors such as dosage, drug release capacity, and properties of PMMA bone cements.[2,10,23,24] The comparison between the use of PMMA with antibiotics and conventional PMMA in cranioplasty is still an area of research that needs attention. Future studies can explore its impact on the prognosis of patients, especially in cases of moderate to extensive defects.[10.23]

The incorporation of 3D printing technology in the production of prefabricated custom cranial implants reveals substantial impact on achieving aesthetically superior results. These benefits include reduced operative time, improved healing, minimized invasiveness, and reduced risk of bleeding. In addition, the ease of reconditioning the personalized implant is noteworthy, using the pre-existing model as a reference.[8,15,16] The proposal for prefabrication of previously sterilized PMMA prostheses emerges as a strategy to reduce operational time, although the strength of the materials and exothermic polymerization continue to be important considerations.[5,25] However, the availability of personalized implants for patients still faces notable restrictions due to the high costs and the long period required for manufacturing, which makes their use in cases of trauma and emergencies impractical. In this scenario, there is still no standard approach established by the medical literature.[5] Recent studies have investigated the application of the CAD/CAM system in the manufacture of PMMA molds for cranioplasty, seeking to improve aesthetics and overcome the limitations inherent to the manual PMMA molding process.[14] The production of custom prefabricated PMMA prostheses, using CAD/CAM, requires computed tomography and sterilization, with the drawbacks of high costs, reported risks of temporal muscle atrophy, and prolonged processes.[2] In pediatric patients, the choice also considers the continuous growth of the skull.[2] The scientific literature has shown successful cases of PMMA application in 3D cranioplasty, supported by several multicenter trials that corroborate the safety and long-term efficacy of these interventions.[5,11] In a retrospective review conducted by Lannon et al.[23] in Canada, the experience in a single center in the use of custom 3D-printed PMMA molds in patients undergoing cranioplasty between 2018 and 2020 was analyzed. The authors highlight the effectiveness in obtaining aesthetic results equivalent to the customized implants commercially available for each patient, while demonstrating a notable decrease in associated costs. Given this scenario, the ultimate strength in custom mold manufacturing through 3D printers is strongly determined by the printing method and parameter adjustments. Material shrinkage and disparities in CAD/CAM software as well as in the post-print procedure are elements that influence accuracy. From this perspective, the application of 3D printers in the manufacture of custom molds stands out as a promising approach, conferring aesthetic benefits equivalent to conventional commercial implants, combined with the associated cost advantage.[11,23]

The progression of biocompatibility, in this sense, emerges as an intrinsic trend in alloplastic materials, and a multidisciplinary approach between medical sciences and engineering is essential.[13,19,24,26] Several characteristics have been proposed to describe the ideal material for cranioplasty, including biocompatibility properties, such as tissue tolerance, simplicity of manufacture, ease of sterilization, low thermal conductivity, radiolucency, lightness, biomechanical reliability, resistance to infections, absence of heat dilatability, low cost, and readiness for use. However, no material perfectly meets all these criteria. In bone cement research, the focus is on optimizing mechanical quality, flexural strength, and compressibility, curing time, and biocompatibility, with an emphasis on biomaterials that effectively stimulate bone growth.[8,19,24]

Additives are investigated to overcome challenges such as loosening of prostheses, high rates of postoperative infection, and compromised interface integrity due to inflammation. The brittleness of bone cement, attributed to additives such as barium sulfate and zirconium oxides, increases the risk of loosening. Stabilizing the die reduces cracking, but decreasing viscosity can compromise mechanical strength.[8,13,19,24,26] When evaluating biocompatibility, several parameters require detailed analysis, including tissue tolerance, ease of sterilization, possible allergic reactions, efficacy in promoting early revascularization, resistance to thermal damage during surgery, thermal conduction capacity, and resistance to the occurrence of infections.[8] The transition from PMMA bone cement to bioactive formulations requires comparable handling characteristics, mechanical improvements and, above all, high osteoconductive and osteoinductive capacity. The lack of osseointegration of PMMA results in the formation of a connective tissue layer between bone and cement,

presenting significant clinical challenges. An additional concern lies in the maximum polymerization temperature, reaching up to 100°C due to the polymerization process of methyl methacrylate (MMA) monomers, with a potential risk of tissue necrosis.[5,9,19,21] In this context, studies investigate the incorporation of bioactive inorganic fillers, such as bioactive glass (BGs), vitreous ceramics, and hydroxyapatite, into the PMMA matrix, seeking to balance improvements in bioactivity with the preservation of mechanical and handling properties.[19] In vitro research conducted by Cui et al.[19,] was performed to optimize bone regeneration through the doping of strontium (Sr) into bioactive borate (BG) glass and its incorporation into PMMA, resulting in the production of bioactive borate compound cements doped with Sr (SrBG)/PMMA. The promising results indicated a significant reduction in the polymerization temperature compared to PMMA, with the maintenance of essential properties, such as adequate adjustment time and mechanical resistance. In addition, there was a notable improvement in osseointegration and regenerative potential compared to PMMA bone cement. In analysis in vitro confirmed the bioactivity of the material with the formation of hydroxyapatite on the surface in a rat tibia model. X-ray diffraction and scanning electron microscopy analyses indicated that the hydroxyapatite was not fully crystallized, presenting nanometric dimensions. These results suggest possible benefits for cell displacement and migration due to the higher surface area and degradation rate. The ions released from SrBG in the composite cements were considered beneficial for the fixation, proliferation, and differentiation of osteoblasts, conferring greater osteogenic capacity in vivo. The authors also highlighted the agreement of these results with previous research. However, further studies on post-implantation composition and the conduct of biomechanical tests are still needed to assess local mechanical stability.[19]

Thus, despite the efficacy in improving bioactivity, it is important to note that the inclusion of these fillers can also compromise fundamental properties, which highlights the need for a balanced approach in research to develop ideal alternatives.[19] The main challenge is to find a balance between improving bioactivity and preserving essential characteristics for clinical application, such as porosity, thickness, biocompatibility and antibacterial properties, making additional and continuous investigations essential, aiming at the successful evolution of bone cements.[13,19,24]

CONCLUSION

In summary, a comprehensive analysis reveals important developments in the field of cranioplasty. Innovative strategies, such as the incorporation of antibiotics into PMMA, stand out as effective measures in reducing infectious complications after cranioplasty, particularly in regions with limited resources. The introduction of 3D printing technology and the manufacture of custom prefabricated implants have demonstrated positive impacts on aesthetics and long-term efficacy, although challenges related to production time and costs, still persist. The incessant search for the evolution of the biocompatibility of alloplastic materials, especially in the context of bone cement, shows growing interest in biomaterials to improve clinical practice. The progressive replacement of PMMA by bioactive versions aims to improve the bone-cement interface and reduce bone resorption, although challenges regarding osseointegration and the high polymerization temperature persist. Ultimately, continuous research and the adoption of innovative approaches are crucial to overcome existing limitations, enhance biocompatibility, and elevate the clinical efficacy of implant materials, enabling remarkable advances in the field of cranioplasty.

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Viviane Aline Buffon: Formal analysis, Methodology
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BioSCIENCE Review Article
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Therapeutic potential of video games for children with mild autism: systematic review of social, motor, and behavioral outcomes

Potencial terapêutico dos videogames para crianças com autismo leve: revisão sistemática de resultados sociais, motores e comportamentais

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ABSTRACT

Introduction: The prevalence of screen time among children has increased significantly, raising questions about its effects on children diagnosed with Autism Spectrum Disorder (ASD), especially those with mild or high-functioning autism. Video games and other digital platforms, often seen as recreational, may have therapeutic potential, engaging children in ways that traditional therapies may not reach.

Objective: To examine the current evidence on the use of video games as therapeutic tools for children with mild ASD, focusing on outcomes such as the development of social and motor skills, the reduction of repetitive behaviors, and the alleviation of anxiety.

Method: A systematic search of the Cochrane, PubMed, and Embase databases identified 7 studies that met the inclusion criteria, totaling 343 participants.

Result: The findings indicate that structured interventions with video games can improve social and motor skills, in addition to reducing repetitive behaviors. Despite the heterogeneity of interventions and outcome measures, the review reinforces the potential of video games as an adjunctive therapy for children with mild ASD.

Conclusion: Further research with standardized protocols and larger sample sizes is recommended to assess long-term efficacy and optimize their integration into therapeutic practices. This review contributes to the growing debate on digital therapies in the management of ASD, highlighting the need for more rigorous and targeted studies.

KEYWORDS: Autism spectrum disorder. Mild autism. Video games. Therapeutic intervention. Social skills. Motor skills. Repetitive behaviors. Screen time. Digital therapeutics.

Central Message

Video games can play a therapeutic role for children with mild autism, aiding in the development of social and motor skills, as well as reducing repetitive behaviors and anxiety. While the growing prevalence of screen time raises concerns, the review's findings suggest that structured video game interventions could be a promising complementary tool for managing Autism Spectrum Disorder (ASD).

Perspective

This article is exploratory and analytical, emphasizing the need for more rigorous research to standardize protocols, assess long-term efficacy, and integrate these digital approaches into traditional therapies. The study contributes to the ongoing discussion about digital therapeutics in the treatment of ASD, highlighting the potential of video games as an innovative and accessible resource.

RESUMO

Introdução: A prevalência do tempo de tela entre crianças tem aumentado, levantando questões sobre seus efeitos naquelas diagnosticadas com Transtorno do Espectro Autista (TEA), particularmente crianças com autismo leve ou de alto funcionamento. Os videogames e outras plataformas digitais, muitas vezes vistos como recreativos, podem ter potencial terapêutico, envolvendo as crianças de maneiras que as terapias tradicionais não podem.

Objetivo: Examinar as evidências atuais sobre videogames como ferramentas terapêuticas para crianças com TEA leve, com foco em desfechos como desenvolvimento de habilidades sociais e motoras, redução de comportamentos repetitivos e alívio da ansiedade.

Método: A busca sistemática nas bases de dados Cochrane, PubMed e Embase identificou 7 estudos que atenderam aos critérios de inclusão, com 343 participantes no total.

Resultado: Os resultados indicam que intervenções estruturadas em videogames podem melhorar as habilidades sociais, as habilidades motoras e reduzir comportamentos repetitivos. Apesar da heterogeneidade das intervenções e medições de resultados, a revisão apóia o papel potencial dos videogames como terapia adjuvante para crianças com TEA leve.

Conclusão: Recomenda-se mais pesquisas com protocolos padronizados e amostras maiores para avaliar a eficácia a longo prazo e otimizar a integração nas práticas terapêuticas. Esta revisão contribui para o crescente discurso sobre a terapêutica digital no gerenciamento de TEA, ressaltando a necessidade de estudos mais rigorosos e direcionados.

PALAVRAS-CHAVE: Transtorno do espectro autista. Autismo leve. Videogames. Intervenção terapêutica. Habilidades sociais. Habilidades motoras. Comportamentos repetitivos. Tempo de tela. Terapêutica digital.

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INTRODUCTION

The increasing prevalence of screen time among children has raised concerns about its impact, particularly for those diagnosed with Autism Spectrum Disorder (ASD). Among individuals with mild forms of autism, also referred to as high-functioning autism, there is growing interest in the potential of video games and digital platforms to serve as therapeutic tools. These games can engage children in a way that traditional therapeutic methods may not, making them a subject of increasing research attention. With a significant number of children with ASD spending considerable time on screens, understanding whether video games can provide more than mere entertainment is essential.[1,2]

Despite the concerns regarding excessive screen time, the potential for therapeutic video games to enhance the developmental trajectories of children with mild ASD presents a unique opportunity. Video games, especially those designed with therapeutic intent, offer a structured, immersive environment where social and motor skills can be honed, and repetitive behaviors, characteristic of ASD, might be reduced. Given the complexity of ASD and the variety of interventions available, it is crucial to evaluate the effectiveness of such targeted interventions, ensuring that this growing screen time is beneficial rather than detrimental.[3,4]

The objective of this article is systematically review the current evidence on the use of video games as a therapeutic tool for children with mild ASD. This review aims to determine whether video games can improve social skills, enhance motor skills, reduce repetitive behaviors, and alleviate associated anxiety. The paper seeks to contribute to the ongoing conversation about therapeutic strategies in ASD care providing a comprehensive analysis of the role of video games as a therapeutic intervention for children with mild ASD, with a focus on key developmental outcomes.

METHOD

This study is a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research question follows the PICOT framework (Population, Intervention, Comparison, Outcome, Time)[5] were: 1) Population (P) refers to children diagnosed with mild ASD, including high-functioning autism and mild autism, were the primary population of interest; keywords for this population included "autism spectrum disorder", "ASD", "mild autism", and "gigh-functioning autism"; 2) Intervention (I): the intervention evaluated was the use of video games and other forms of screen-based stimulation as therapeutic tools and included traditional video games, serious games, therapeutic video games, gaming therapy, and computer-based games, all aimed at improving skills and behaviors in children with mild ASD; 3) Comparison (C): consisted of children with ASD who did not receive video game-based interventions and this group either had no intervention or received standard care, which could include behavioral therapy without the use of video games or screen-based stimulation; 4) Outcome (O): the primary outcomes evaluated were the improvement of social and motor skills, the reduction of repetitive behaviors, and the alleviation of anxiety, and additional outcomes included overall behavioral therapy success and cognitive enhancement in the children receiving video game-based therapy; 5) Time (T): the studies selected for inclusion varied in follow-up duration, with no specific time limit enforced for the analysis due to the indeterminate follow-up periods across the trials. The focus was placed on randomized controlled trials (RCTs), providing high-quality evidence on the efficacy of video game-based interventions.

Search strategy

The databases searched included Cochrane, PubMed, and Embase, using a broad range of terms related to ASD and video game interventions. Search terms combined both MeSH headings and free-text words such as "Autism Spectrum Disorder", "ASD", "Video games", "Screen time", and "Therapeutic video games". Boolean operators and truncation were employed to maximize the retrieval of relevant studies.

Inclusion criteria

The inclusion criteria required that studies involve children with mild ASD, and report on outcomes related to social and motor skill development, repetitive behaviors, or anxiety. No time or language restrictions were applied. Data extraction was performed by two independent reviewers, and any discrepancies were resolved through discussion and consultation with a third reviewer. The quality of the included studies was assessed using the Cochrane Risk of Bias tool (Figure).

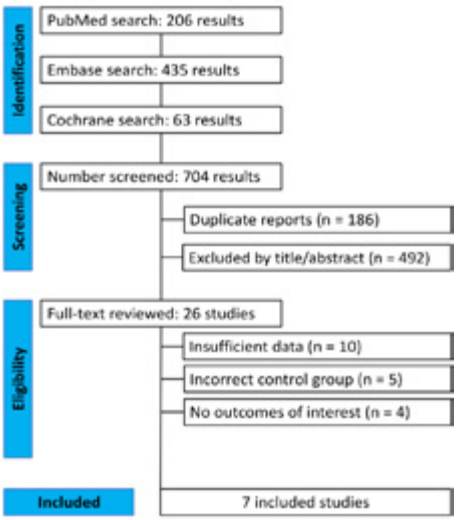

FIGURE — PRISMA flow diagram of study screening and selection

DISCUSSION

The search yielded 704 records: 63 from Cochrane, 206 from PubMed, and 435 from Embase. After the removal of 186 duplicates, 518 records were screened for eligibility using a double-blind process. Of these, 26 studies were read in full, but 5 were excluded due to incorrect control group criteria, 10 to insufficient data and 4 due to no outcomes of interest, leaving 7 studies for final

inclusion in the systematic review. Total of the 7 studies included 343 patients from 294 RCTs, and 49 non-randomized cohorts (Table). The included articles were: Shamir 2022[6], Jouen 2017[7], Kirst 2022[8], Scherf 2021[9], Serret 2017[10], Milajerdi 2021[11], and Dickinson 2016[12].

A deeper analysis of the studies included in the systematic review reveals several important insights regarding the use of video games as a therapeutic intervention for children with mild ASD.

The studies generally involved children diagnosed with mild ASD or high-functioning autism, but the homogeneity of the samples may limit the generalizability of findings to the broader spectrum of ASD. Additionally, the predominance of male participants (e.g., Shamir et al. and Jouen et al. had 100% male participants[6,7]) reflects the higher prevalence of ASD in males but raises concerns about the applicability of findings to female children, who may exhibit different social and behavioral patterns in response to video game interventions.

Interventions varied significantly across studies, from more structured, therapeutic video games designed specifically to improve social and cognitive functions[8] to less structured screen time exposures or digital games.[9] The structured games often involved metacognitive guidance, meaning they were explicitly designed to engage the participants in self-reflective thinking about their social behaviors. These guided interventions are more likely to yield improvements in targeted outcomes, such as eye-contact duration or total gazing time.[6]

The level of engagement required by the participants also varied. More interactive games, especially those incorporating serious games with therapeutic components, tend to actively involve participants in scenarios where they practice social skills in a simulated environment. Passive screen time, or games lacking a social component, are less likely to produce meaningful social improvements. Studies like Jouen et al. in 2017[7], which used both a control and a game intervention,7 (Goliah combined with TAU), highlight the benefits of coupling game-based therapy with traditional therapeutic interventions. This suggests that video games should be seen as adjunct rather than a standalone treatment.

Several studies focused on social skills improvement, which is a core challenge for individuals with ASD. Shamir et al.[6] reported significant improvements in eye-contact duration and total gazing time, indicating enhanced social engagement. Other studies, such as Kirst et al.[8,] measured broader social skills improvements using standardized tools like ADOS (Autism Diagnostic Observation Schedule), confirming that targeted video games can lead to measurable social enhancements. However, the clinical significance of these improvements remains unclear, as none of the studies examined the long-term retention of these skills beyond the intervention period.

Studies like Griffin et al.[9] emphasized motor skills improvements, particularly hand-eye coordination, and fine motor abilities, which are often delayed in children with ASD. These findings align with previous research on the motor benefits of video games, suggesting that certain types of games can be used to promote motor development in this population.

Repetitive behaviors, another hallmark of ASD, were less frequently measured across the studies. However, Kirst et al.[8] included measures of repetitive behavior reduction, which, while not as prominent an outcome as social skills, still highlights the potential for video games to modulate ASD symptoms beyond the social domain. This could have significant implications for the development of therapeutic interventions targeting the broader spectrum of ASD behaviors.

The heterogeneity of video game interventions presents a challenge when synthesizing the findings. The studies used different types of video games, ranging from serious therapeutic games to more general commercial video games, which limits the ability to draw firm conclusions about which specific game characteristics (e.g.[9,] interactivity, feedback, narrative structure) are most beneficial for children with ASD. For instance, some games involved significant social interaction components, while others focused solely on motor or cognitive stimulation.

The tools used to measure outcomes varied, with

TABLE — Seven studies were included for final evaluation in this systematic review

Characteristic	Design	nº Patients	Intervention (IT)	Control (CT)	Sex	Age
Study		(n)	(n ; %)	(n ; %)	(n ; %)	M (SD)
Shamir 2022	RCT	18	with metacognitive guidance (9 ; 50%)	without metacognitive guidance (9 ; 50%)	M (18 ; 100%)	91.66 (14.26) (months)
Jouen 2017	non-RCT	24	GOLIAH + TAU (14 ; 58.3%)	TAU (10 ; 41.7%)	M (24 ; 100%)	IT: 6.85 (1.34) CT: 7.17 (1.62) (probably years)
Kirst 2022	RCT	82	Zirkus Empathico (42 ; 51.22%)	Condition (40 ; 48.78%)	IT: M (32 ; 76.2%) CT: M (37 ; 92.5%)	IT: 8.1 (1.6) CT: 7.6 (1.3) (years)
Griffin 2021	RCT	34	Serious Game (14 ; 41.2%)	Standard Care (20 ; 58.8%)	IT: M (12 ; 85.7%) CT: M (17 ; 85%)	IT: 163.8 (31.9) CT: 168.4 (36.9) (months)
Serret 2017	non-RCT	25	with SEMA-TIC (12 ; 50%)	without SEMA-TIC (13 ; 50%)	IT: M (11 ; 91.7%) CT: M (9 ; 69.2%)	IT: 8.7 (1.0) CT: 8.5 (1.8) (years)
Milajerdi 2021	RCT	60	Kinect (20 ; 33%)	SPARK (20 ; 33%); Control (20 ; 33%)	IT: M (19 ; 95%) CT: M (19 ; 95%) S (19 ; 95%)	IT: 8.45 (1.50) CT: 8.15 (1.45) S: 7.95 (1.60)
Dickinson 2016	RCT	100	Nintendo (50 ; 50%)	without Nintendo (50 ; 50%)	IT: M (39 ; 78.0%) CT: M (40 ; 80.0%)	7 – 16 yo

some relying on parent-reported outcomes, which are subject to bias, while others used more objective behavioral assessments, such as eye-tracking for social gaze measurements.[6] The variability in measurement tools introduces inconsistency in how outcomes are defined and measured, making it difficult to compare results across studies.

The studies suggest that video games, particularly those designed with therapeutic goals, offer a promising avenue for enhancing social skills and motor development in children with mild ASD. However, their clinical relevance needs to be further substantiated with larger, more homogenous samples and standardized interventions. Additionally, future studies should explore how individual differences in game engagement, such as baseline cognitive abilities or interest in gaming, might moderate treatment outcomes. This would help tailor interventions more effectively to individual patient needs.

Further research should also investigate the integration of video games with traditional therapeutic modalities, as suggested by Jouen et al.[7,] maximizing therapeutic outcomes. Combining video games with cognitive-behavioral therapy or social skills training could yield synergistic effects that neither intervention can achieve on its own.

While the reviewed studies offer preliminary evidence supporting the use of video games as a therapeutic tool for children with mild ASD, further research is needed to standardize intervention protocols and assess long-term outcomes. The potential for video games to address core ASD challenges, such as social skills deficits and repetitive behaviors, is promising, but more rigorous trials with larger sample sizes and longer follow-up periods are essential to confirm these findings.

In the realm of therapeutic interventions for children with ASD, recent studies underscore the growing recognition of digital therapeutics (DTx) and serious games as promising strategies. These approaches aim to address social communication challenges and improve social skills among children diagnosed with ASD.

One notable review evaluated the effectiveness of serious games in enhancing social skills among children and adolescents with ASD. The findings highlighted a positive impact on various aspects of social functioning, including emotional recognition, joint attention, and behavioral skills.[13,14]

This aligns with the outcomes of this systematic review, which noted improvements in social skills, motor skills, and reductions in repetitive behaviors through gaming therapy. Additionally, emerging technologies such as virtual reality and artificial intelligence are gaining traction in the field of digital therapeutics. A bibliometric analysis revealed that these technologies are becoming increasingly integrated into interventions for ASD, allowing for more personalized and effective treatment options.[13]

Overall, the intersection of video games, digital therapeutics, and ASD treatment represents a dynamic area of research that holds promise for improving the quality of life for affected children and their families. As more studies emerge, they will further elucidate the efficacy and mechanisms behind these innovative therapeutic approaches. Future research should focus on larger, more homogenous samples, standardized intervention protocols, and extended follow-up to fully assess the enduring effects of video game interventions on children with ASD.

Despite these promising results, several limitations must be acknowledged. The heterogeneity of study designs, the variability in outcome measurement tools, and the short duration of follow-up periods hinder the generalizability and long-term applicability of the findings.

CONCLUSION

This systematic review highlights the emerging role of video games as a therapeutic intervention for children with ASD. The findings from the 7 included studies indicate that structured video game interventions can lead to significant improvements in social skills, motor skills, and reductions in repetitive behaviors. Moreover, the evidence suggests that video games not only provide an engaging platform for skill development but also hold promise for improving cognitive functions and reducing anxiety in children with ASD. While video games offer a novel and potentially effective approach for enhancing the therapeutic landscape for children with mild ASD, further rigorous studies are needed to validate these findings and explore the optimal integration of gaming into existing therapeutic frameworks. As digital technologies continue to evolve, they present exciting opportunities for improving the quality of life for children with autism and their families.

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