ISSN online 2764-9350
ISSN impresso 2764-9342

BioSCIENCE

Volume 83 / 2025

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BioSCIENCE

Orgão oficial da Associação Médica do Paraná
Fundada em 1937, pelo Prof. Milton Macedo Munhoz
BioSCIENCE é a continuação do título Revista Médica do Paraná, fundada em 1933. É publicada em fluxo contínuo e é de responsabilidade da Associação Médica do Paraná

CONSELHO EDITORIAL

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BioSCIENCE Editorial
https://doi.org/10.55684/2025.83.e0001

Gene editing and CRISPR: are we prepared for its ethical implications?

Edição genética e CRISPR: estamos preparados para suas implicações éticas?

Jorge Hernández Navas[1], Juan Therán Leon[1]

KEYWORDS: Gene editing. CRISPR. Ethics.
PALAVRAS-CHAVE: Edição genética. CRISPR. Ética.

Gene editing, led by tools such as CRISPR-Cas9 (a genetic engineering tool that allows researchers to modify DNA in living organisms), has transformed molecular biology by offering a precise, efficient, and relatively affordable method for modifying the genome of living organisms. Since its discovery, this technology has opened up a range of possibilities in fields as diverse as medicine, agriculture, and basic research, consolidating it as one of the greatest scientific innovations of the twenty-first century. However, this dizzying advance has generated intense ethical, legal and social debates that require collective reflection and establishment of appropriate regulations.[1]

In medical field, CRISPR-Cas9 has shown to be a promising tool for treating genetic diseases previously considered incurable. The correction of mutations in genes responsible for diseases such as cystic fibrosis, sickle cell anemia or Huntington's disease is already beginning to materialize in preclinical research and clinical trials. In addition, this technology has enabled significant advances in cancer immunotherapy and the development of organs for transplants through animal cell editing. In the agricultural sector, it has contributed to the development of crops that are more resistant to pests, droughts, and adverse weather conditions, which can help combat global food insecurity.[2]

However, CRISPR is not foolproof. Off-target effects, which consist of unintended genetic changes, pose significant risks. These mistakes can lead to unexpected consequences, from cell damage to the development of new diseases. In the case of gene editing in humans, these risks become even more critical, as they can be passed on to future generations if germline cells are modified. Therefore, it is essential to conduct extensive research, as well as rigorous preclinical and clinical trials, before applying these technologies in a widespread manner.[3]

The use of CRISPR for human germline editing, which entails the modification of embryos and the possibility of altering hereditary traits, is one of the most controversial aspects of this technology. While it can prevent devastating genetic diseases, it also raises deep ethical concerns by opening the door to the creation of "designer babies." This can result in the selection of traits such as intelligence, eye color, or physical performance, raising fundamental questions about the boundaries between legitimate medical treatment and genetic enhancement. The question arises of who should decide which modifications are acceptable and how to prevent this technology from perpetuating or exacerbating existing social inequalities.[3]

From a global perspective, inequalities between developed and developing countries are worrying. In many regions, a lack of scientific infrastructure and limited regulatory capacity may leave them behind in accessing and controlling this technology, perpetuating an already considerable innovation and health gap. In addition, the irresponsible use of CRISPR by unregulated actors can lead to ethically questionable experiments with potentially catastrophic consequences.[3]

It is essential to establish a global regulatory framework that guarantees the safe, ethical, and equitable use of gene editing. This requires active collaboration between scientists, bioethicists, policymakers, and civil society. Governments should work with international organizations, such as UNESCO or the World Health Organization (WHO), to develop guidelines that limit the unethical use of CRISPR, promote transparency in research, and ensure equitable access to its benefits. Public

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Conflict of interest: None | Funding: None | Received: 07/10/2024 | Accepted: 09/12/2024 | Publication date: 11/02/2025 | Correspondence: jorgeandreshernandez2017@gmail.com | Associate Editor: Carmen Australia Paredes Marcondes Ribas

How to cite:
Navas JH, Leon JT. Edição genética e crispr: estamos preparados para suas implicações éticas?. BioSCIENCE. 2025;83:e00001

education also plays a crucial role. It is essential to foster informed and participatory debate so that decisions about the use of CRISPR are not exclusively in the hands of experts, but include the perspectives of the whole society.[4]

While gene editing through tools like CRISPR-Cas9 represents a scientific revolution with the potential to transform medicine and society, this power carries significant responsibility. Moving forward with caution is essential, prioritizing the safety of patients and the well-being of future generations. Only through a balanced approach, which combines scientific innovation with a solid ethical and social basis, will it be possible to maximize the benefits of this revolutionary technology while minimizing its risks. Open dialogue, strict regulation, and a commitment to equity will be key to ensuring that gene editing becomes a tool at the service of all humanity, and not an exclusive privilege of few.[5]

Authors' contributions

Jorge Hernández Navas: Conceptualization, Project administration, Writing (review and editing)

Juan Therán Leon: Conceptualization, Project administration, Writing (original draft), Writing (review and editing)

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BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e00002

Does anatomical recognition of the innervation of the inguinal region during hernioplasty prevent inguinodynia?A systematic review

O reconhecimento anatômico da inervação da região inguinal durante hernioplastia previne a inguinodinia? Uma revisão sistemática

Ana Júlia Ribas Sigwalt[1], Gabriella Micheten Dias[2], Lívia Dala Déa Ferreira Pocay[3], Mahara Freitas dos Santos[3], Tailla Cristina de Oliveira[3], Marcos Fabiano Sigwalt[2,3], Fernando Issamu Tabushi[3,4], Leonardo Wanderloff Franco[3], Fernando Weiss Guerra[5], Abdo Imad El Tawil[3], Osvaldo Malafaia[3]

ABSTRACT

Introduction: The inguinal canal is a region prone to hernias that may require surgery. Although videosurgery may be less aggressive, the identification of nerve branches is necessary to reduce the incidence of inguinodynia that can occur even with this minimally invasive route.

Objective: To review the incidence and reasons for inguinodynia in laparoscopic surgical procedures for the correction of inguinal hernias.

Method: Systematic review, carried out in the PubMed, BVS and Google Scholar databases from 2018 to 2024, including articles in Portuguese and English. From initial number of 1,758 articles 10 were selected.

Result: The main findings of the research proved that the recognition and proper anatomical identification of the main nerves of the inguinal region during the operation - iliohypogastric, ilioinguinal and genital branch of the genitofemoral - are able to reduce the chances of patients developing chronic pain in the inguinal region after hernioplasty. The surgeon's expertise and experience in avoiding trauma to local nerves guarantees quality of life for patients and reduces their exposure to possible new subsequent interventions to treat inguinodynia.

Conclusion: Prevention is the most important measure when it comes to eradicating inguinodynia. Therefore, the professional must have sufficient knowledge of the most frequent topography of the passage of the main nerves and their branches to avoid iatrogenic injuries

KEYWORDS: Inguinal hernia. Nerve identification. Inguinodynia. Surgery.

RESUMO

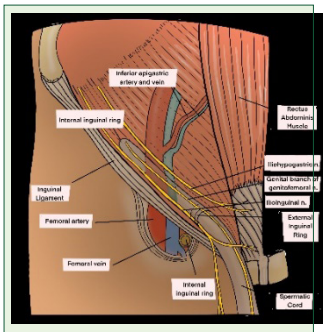
Introdução: O canal inguinal é região propensa a hérnias que podem ter indicação cirúrgica. Embora a videocirurgia possa ser menos agressiva, a identificação dos ramos nervosos é necessária para diminuir a incidência de inguinodinia que pode ocorrer mesmo com essa via minimamente invasiva.

Objetivo: Revisar a incidência e os motivos da inguinodinia nos procedimentos cirúrgicos laparoscópicos na correção das hérnias inguinais. Método: Revisão sistemática, realizada nas bases de dados PubMed, BVS e Google Scholar no período de 2018 a 2024, incluindo artigos em português e inglês. De 1.758 artigos, 10 foram selecionados.

Resultado: Os principais achados da pesquisa comprovaram que o reconhecimento e a devida identificação anatômica dos principais nervos da região inguinal durante a operação – ílio-hipogástrico, ilioinguinal e ramo genital do genitofemoral - são capazes de diminuir as chances de os pacientes desenvolverem dor crônica na região inguinal após hernioplastia. A perícia e experiência do cirurgião ao evitar trauma nos nervos locais garante qualidade de vida aos pacientes e reduz a exposição deles a eventuais novas intervenções subsequentes para tratamento de inguinodinia.

Conclusão: A prevenção é a medida mais importante tratando-se de erradicar a inguinodinia. Dessa maneira, o profissional deve ter conhecimento suficiente da topografia mais frequente da passagem dos principais nervos e seus ramos para evitar lesões iatrogênicas.

PALAVRAS-CHAVE: Hérnia inguinal. Identificação do nervo. Inguinodinia. Cirurgia.



Visualization of the inguinal nerves

Central Message

The inguinal canal is a region prone to hernias that may have surgical indication. Although videosurgery may be less aggressive, identification of nerve branches is necessary to decrease the incidence of inguinodynia that can occur even with this minimally invasive route. The objective of this article was to investigate the incidence and reasons for inguinodynia in laparoscopic surgical procedures for the correction of inguinal hernias. This topic is pertinent to the daily routine of the general surgeon because he can, with his knowledge, avoid nerve injuries that cause inguinodynia

Prospective

Surgeons' knowledge of the nervous anatomical region by laparoscopic surgery is capable of preventing inguinodynia. The identification, recognition, and preservation or dissection when necessary of the main nerves in the region prevents chronic groin pain. Therefore, it is understood that with the surgical techniques currently available for hernioplasty, added to the expertise of the professional who performs the procedure, inguinal hernia repair can be mostly effective and without sequelae of chronic pain.

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Conflict of interest: None | Funding: None | Received: 07/010/2024 | Accepted: 09/12/2024 | Publication date: 11/02/2025 Correspondence: marcossigwalt@yahoo.com.br | Associate Editor: Luiz Fernando Kubrusly

How to cite:
Sigwalt AJR, Dias GM, Pocay LDDF, dos Santos MF, de Oliveira TC, Sigwalt MF, Tabushi FI, Franco LW, Guerra LW, El Tawil AI, Malafaia O. O reconhecimento anatômico da inervação da região inguinal durante hernioplastia previne a inguinodinia? Uma revisão sistemática. BioSCIENCE. 2025;83:e00002

INTRODUCTION

The inguinal canal is defined as an area delimited by 3 muscles: external oblique, internal oblique and transversus abdominis. Different structures pass through it, depending on the sex, such as the spermatic cord in men and the round ligament of the uterus in women. Hernia is a common finding in this canal, which occurs due to the weakening of local elastic fibers and collagen.

Inguinal hernia can be classified as direct or indirect, depending on whether its position is medial or lateral in relation to the inferior epigastric vessels.[1] Its repair is the most commonly performed procedure in the surgical environment and widely used laparoscopically, as it has demonstrated significant advantages in the postoperative period, such as rapid recovery, lower occurrence of postoperative pain, and better scores that represent quality of life for patients.[2] In addition, video hernioplasty has been considered superior to open procedures when analyzing the lower risk of trauma to the locoregional innervature, being less invasive and having less traumatic fixation of the mesh in order to reduce postoperative discomfort.[3] However, it does not exclude them, because approximately 6-8% of the 20 million hernioplasties performed annually are associated with problems that affect quality of life, especially chronic post-surgical pain.[4]

During the video procedure, it is possible to observe the various nerves that cross the inguinal canal. The main ones found, and possible to be affected during surgical manipulation, are the iliohypogastric nerve, ilioinguinal nerve and the genital branch of the genitofemoral nerve. These branches come from the lumbar plexus, which is responsible for innervating the lower abdomen; however, when they are distributed individually, they are subject to anatomical variations.[5,6] Although videosurgery has good results, there are postoperative complications such as osteitis pubis, ischemic orchitis, local hematomas, seroma, and, especially, nerve pain. This can be of direct neurological and non-neurological cause (such as periostitis, recurrent hernia and spermatic cord injury). Among them, the most common is due to iatrogenic injury, justified, in most cases, by the failure to identify the nerves of the inguinal region during the procedure, primarily involving the aforementioned nerves.[7-9] After causing trauma or damage to the local innervation, through excessive dissection, crushing, stretching, or mesh placement, the patient usually complains of pain that may be accompanied by other sensory disorders such as dysesthesia, hyperesthesia, hypoesthesia, among others. In addition, this chronic pain, called inguinodynia, affects quality of life and has been associated with psychological and mental disorders after the procedure.[5]

The objective of this review was to analyze whether the anatomical recognition of the sensory innervation of the inguinal region during laparoscopic inguinal hernia repair is able to help prevent chronic postoperative pain, i.e., inguinodynia.

METHOD

This systematic review was based on the guidelines of the PRISMA method (Main Items for Reporting Systematic Reviews and Meta-Analyses), and the guiding question was structured by the acronym PICO: "Is anatomical recognition of the sensory innervation of the inguinal region capable of assisting in the prevention of chronic postoperative pain for laparoscopic inguinal hernia repair?" (Table 1).

TABLE 1 — PICO Survey

P (patient)	Patients with chronic pain
I (intervention)	Submitted to the operation for correction videolaparoscopic inguinal hernia
C (control)	Patients without chronic pain for correction videolaparoscopic inguinal hernia
The (outcome)	Post-corrective operation

The search was carried out in the period from 2018 to 2024. The descriptors used were chosen from the Health Sciences Descriptors (DeCS) dictionary, considering articles in Portuguese and English, with the descriptors and booleans being: inguinal hernia repair; nerve identification, inguinodynia. Priority was given to selecting the articles that had the highest degree of qualification by the EQUATOR Network. In addition, the types of study chosen were: randomized controlled trials, cohort studies, case-control studies, and systematic reviews.

The inclusion criteria were: articles that addressed chronic pain after inguinal hernia repair with the laparoscopic technique, complete articles, free texts and high academic relevance. The exclusion criteria were: studies with the objective exclusively of nerve structures, pediatric population (under 16 years of age) and elderly population (over 60 years of age) exclusively and operations with open techniques.

The final evaluation of the selected articles was carried out using the eligibility criterion using, as a reference, the guiding question of the work. To reduce the risk of bias, the evaluation was done in pairs (in which 2 researchers evaluate and qualify the article, if there was disagreement, the article would be excluded).

The search was carried out on the VHL, Google Scholar and PubMed platforms, following the inclusion and exclusion criteria already described. In the VHL, the initial search resulted in 135 articles, 106 were filtered with the full text, after applying the language filter, 99 remained and only 42 with the filter of the last 5 years. Of these, 19 were used to read the titles and 19 were selected to read abstracts, 5 of which were systematic reviews. In PubMed, 107 appeared with the full-text filter, 97 remained and 34 with the years filter; of these, 11 were selected by reading the titles, 10 by the abstracts, 3 were read in full and only 2 to compose the systematic review. Google Scholar, the initial search resulted in 1,758 articles, after applying the language filter, 1,665 remained and 664 with the filter of the last 5 years; of these, 78 were used after reading the titles and 26 were selected for reading abstracts and only 6 texts remained for this search. In

all, 12 articles were selected; 10 remained for the final reference of this study and 2 were discarded due to duplicity (Figure 1, Table 2).

In the evaluation of the GRADE system (Table 3), the article Caserta et al.[1,] because it is iconographic in which information is taken from the graphs, it had serious indirect evidence, being unreliable. The article Carrillo et al.[4,] the sample size was low.

DISCUSSION

Inguinodynia after videosurgical inguinal hernia repair

Inguinodynia has become the most common long-lasting complication of inguinal hernioplasty. With a prevalence of approximately 20 million hernioplasties performed annually,

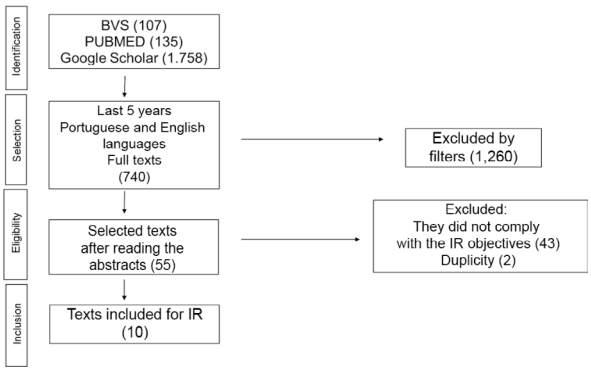


FIGURE 1 — Synthesis of the research

TABLE 2 — Results compiled from the selected articles

AUTHOR AND YEAR	DESIGN OF STUDY	SAMPLE POPULATION	TYPE OF INTERVENTION	CONCLUSIONS
1 - Caserta N. (2021)[1]	Iconographic essay			Knowledge of the presentation of inguinal hernias, their different contents and possible complications is essential for the correct diagnosis and appropriate management.
2 - Dop LMVD. (2022)[2]	Prospective study	Patients undergoing inguinal hernia repair with a minimum of 2 years follow-up. n=4016	TAPP, TIPP. TOE	Postoperative pain after 1 month was a higher risk factor for the development of PIPC than preoperative pain. PIPC at 1 year appears to be a different cause of pain than PIPC at 2 years. Patient and surgical factors influence its onset at 1 year, but the natural course of these complaints shows a large decline at 2.
3 - Mitura K. (2018)[3]	Prospective study	Patients undergoing TAPP repairs n=146	TAPP approach with 3D screen using glue fixation.	TAPP inguinal hernia repair with glue fixation significantly decreased the frequency and intensity of pain compared to that felt preoperatively. Patients younger than 40 years of age have frequent and severe preoperative and postoperative pain. In addition, hernias of longer duration before the operation cause increased pre- and postoperative pain.
4 - Carrillo GG. (2023)[4]	Retrospective study	Patients undergoing transperitoneal neurectomy. age ≥41 years and ≤ 54 years n = 7	Laparoscopic and robotic triple neurectomy for chronic inguinodynia.	Laparoscopic retroperitoneal triple neurectomy is a reproducible, low-morbidity technique that improves symptoms and quality of life of chronic inguinal pain after hernioplasty.
5 - Graham D. (2018)[5]	Review Article			Prevention is the most important measure in mitigating neuropathic PIPC. Recognition of the typical neuroanatomy of the lumbar plexus, the highly variable nature of these nerves, and the operation-specific mechanisms for nerve entrapment will limit the potential for injury and improve outcomes in inguinal hernia repair.
6 - Cirocchi R. (2019)[6]	Systematic review	Articles evaluating the anatomical variations of the inguinal nerves according to PRISMA standards n = 26		The identification rates of inguinal nerves in this study were lower than those reported in the literature. The smallest was found for the genitofemoral nerve, suggesting that this nerve was the most difficult to identify. Knowledge of the anatomy of inguinal nerves can facilitate their proper identification and reduce the risk of iatrogenic injury and postoperative pain.
7 - George T. (2019)[7]	Retrospective review	Patients with persistent groin pain, with relief after preoperative nerve block and failed attempt at external denervation of the groin or pain after hernia repair.n=16	Primary laparoscopic inguinal hernia repair TAPP or PTE.	A combined open surgical procedure to identify the lateral femoral cutaneous nerve and 1 laparoscopic procedure in the retroperitoneum demonstrated the feasibility of this approach to correctly identify the nerve to be resected to relieve disabling groin pain.
8 - Farquharson BJ. (2021)[8]	Retrospective review	District general hospital patients Age ≥18 years and <80 years n = 100	Open inguinal hernia repair with prosthetic mesh.	Further analysis of the implications for chronic postoperative pain, along with best practices and forensic medical litigation, would be beneficial in improving documentation standards.
9 - Pedersen, RF. (2020)[9]	Prospective study	Patients for chronic posthernia repair pain operation. n= 66	Open triple neurectomy with total mesh removal or laparoscopic retroperitoneal triple neurectomy.	Pain-related functional impairment can be improved with clinical relevance by approximately 70% through a simplified clinical algorithm for surgical treatment of severe chronic pain after inguinal hernia repair.
10- Furtado M. (2019)[10]	Original article		Dissection of the preperitoneal space using the TAPP approach.	The concept of "Inverted Y" and the anatomical didactics "Five Triangles" associated with the dissection proposal based on "Three Zones", meets the need to establish standardization of the TAPP technique, seeking excellence in the results of inguinal treatment.

IPFC = chronic postoperative inguinal pain; TAPP=Lichtenstein; TIPP=transinguinal preperitoneal repair; PTE=totally extraperitoneal

TABLE 3 — Evaluation of the quality of the articles by the GRADE scale

AUTHORS/ CRITERIA	1 - Caserta N. (2021)1	2 - Dop LMVD. (2022)2	3 - Mitura K. (2018)3	4 - Carrillo GG. (2023)4	5 - Graham D. (2018)5	6 - Cirocchi R. (2019)6	7 - George T. (2019)7	8 - Farquharson BJ. (2021)8	9 - Pedersen, RF. (2020)9	10 - Furtado M. (2019)10
RISK OF BIAS	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG
INCONSISTENCY	NG	NG	NG	G	NG	NG	NG	NG	NG	NG
INDIRECT EVIDENCE	G	NG	NG	NG	NG	NG	NG	NG	NG	NG
INACCURACY	NG	NG	NG	NG	NG	NG	NG	NG	NG	NG

NG=not severe; G=severe

between 6-8% of them are associated with problems that affect the patient's quality of life.[4] The onset of inguinodynia is influenced by gender and age, and the nature of the operation, including the type of fixation and management of the nerves.[2] However, chronic postoperative inguinal pain can develop after all hernia repair methods and is independent of the technique, and can be nociceptive or neuropathic in nature. Nociceptive pain is caused by actual damage to non-neural tissue, such as musculoskeletal inflammation, while neuropathic pain is defined as injury or damage to the nervous system. Thus, research has already concluded that the main cause related to this pain is the failure to identify the inguinal nerves.[5]

Inguinal neuroanatomy is complex and very variable, from the retroperitoneal lumbar plexus to the terminal branches that exit through the inguinal canal. The most commonly affected in this pain are the iliohypogastric, ilioinguinal, and genital branches of the genitofemoral nerve. Although not so frequent, the lateral femoral cutaneous nerve, the femoral branch of the genitofemoral nerve, and the obturator nerve can also be injured in the preperitoneal space.[5] Thus, success in the surgical identification of the 3 nerves is associated with surgical skills, but sometimes some anatomical variations make it difficult to identify them, regardless of the skill level, especially in cases where some of the inguinal nerves are not present. For these reasons, it is necessary to standardize education and training in the identification of nerves in hernioplasty.[6]

Neuroanatomy of the inguinal region

The inguinal canal is defined as 2 openings with 1 deep inner ring at the midpoint of the inguinal ligament and 1 superficial outer ring that is superior to the pubic tubercle. The posterior wall of this canal is defined by the lateral transverse fascia and the conjunct tendon medially, and the anterior wall is composed of an external oblique aponeurosis reinforced laterally by the internal oblique muscle.[5] The lower portion of the floor is composed of the inguinal ligament, which is reinforced medially by the lacunar and pectineal ligaments. The content of this canal is the spermatic cord (male) and the round ligament (female), and it is also crossed by the iliohypogastric and ilioinguinal nerves and the genital branch of the genitofemoral nerve. These nerves are the terminal branches of the lumbar plexus, which is located in front of the transverse processes of the lumbar and posterior vertebrae or within the psoas muscle, and innervate the abdominal muscle and skin of the genitals, buttocks, and hypogastric region. The schematic drawing of the inguinal region and its nerves can be seen in Figure 2.

The iliohypogastric nerve is a mixed sensorimotor nerve and originates from the ventral branch of L1, emerging from the superior lateral border of the psoas major muscle, passing over the quadratus lumborum, and entering the transversus abdominis muscle above the iliac crest. It divides into 1 lateral cutaneous branch, which passes between the internal and external oblique muscles, above the iliac crest, and innervates the posterolateral gluteal skin, and 1 anterior branch, which runs between the transversus and the internal oblique, responsible for the innervation of both muscles, between the transverse and internal oblique muscles. Then, when it exits the internal oblique muscle, it passes inside the inguinal canal, prior to its exit through the external oblique, approximately 3 cm above the superficial outer ring in the inguinal sickle.[5]

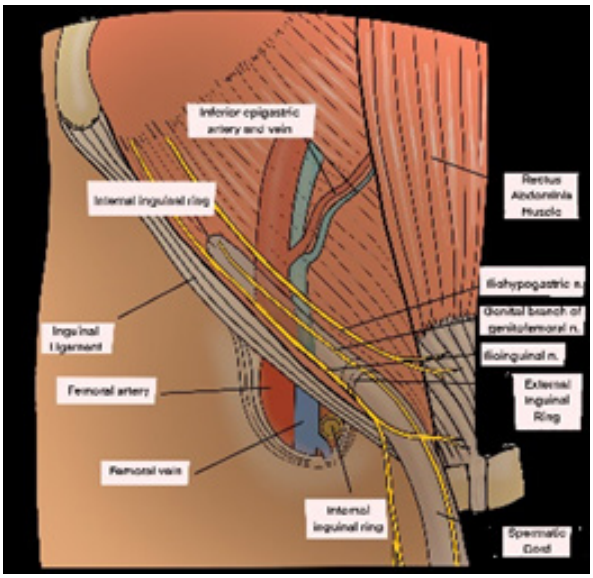
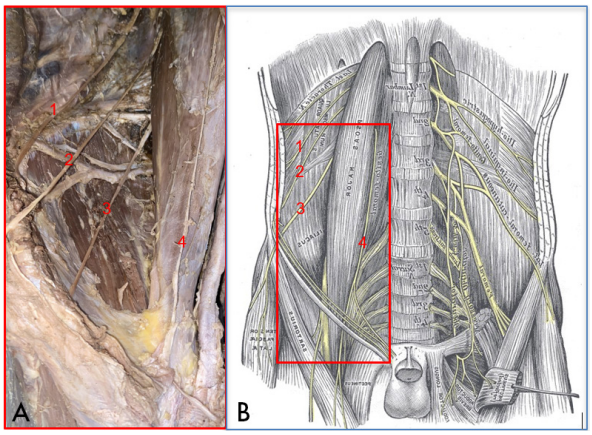


FIGURE 2 — Nerves of the inguinal region: anatomical schematic drawing

The ilioinguinal nerve is a mixed sensorimotor nerve that arises from the first ventral lumbar branch and emerges from the superolateral border of the psoas muscle. It runs through the quadratus lumborum muscle and the upper part of the iliacus and finally enters the transversus abdominis muscle near the iliac crest. It innervates the internal oblique muscle and perforates below the iliohypogastric, approximately 1 cm medial to the anterior superior iliac spine. It normally runs along the spermatic cord, exiting through the superficial outer inguinal ring to supply the proximal medial skin of the thigh and inguinal fold in both sexes, and the superior scrotal region and lateral base of the penis.[5]

The iliohypogastric and ilioinguinal nerves can be clearly visualized in Figure 3.



Source: adp. Henry Gray's Anatomy of the Human Body

FIGURE 3 — A) Cadaveric visualization: iliohypogastric nerve (1), ilioinguinal nerve (2), lateral cutaneous femoral nerve (3) and genitofemoral nerve (4); B) drawing demonstrating their relationship with the abdominoinguinal region

The genital branch of the genitofemoral nerve, in turn, is a mixed sensorimotor branch originating from the ventral

branches L1 and L2 and forms within the psoas muscle, emerging at its medial border between the L3 and L4 levels. It descends below the peritoneum, passes posteriorly to the ureter, and moves towards the inguinal ligament. The genital branch typically passes over the external iliac artery and crosses the deep internal inguinal ring to join the structures of the cord or round ligament before entering the inguinal canal. In men, it provides motor innervation to the cremaster muscle and cutaneous sensation of the upper scrotum. In women, it follows the round ligament and innervates the skin of the mons pubis and labia majora.[5] The femoral branch, which is rarely affected, descends laterally to the medullary structures and iliac vessels, passing under the inguinal ligament. It enters the femoral sheath lateral to the femoral artery and then pierces the femoral sheath and fascia latae to supply the skin of the upper anterior thigh over the femoral triangle.[5]

The lateral femoral cutaneous nerve is a sensory nerve with great variability in its origin and course. It usually originates from the posterior division of the 2nd and 3rd lumbar nerve roots, emerges from the lateral border of the psoas muscle below the iliac crest, and passes behind the peritoneum over the iliac muscle obliquely towards the anterosuperior iliac spine. The nerve then passes behind or through the inguinal ligament approximately 1 cm medial to the anterosuperior iliac spine, travels anteriorly or through the sartorius muscle before dividing into superficial anterior branches, which irrigates the anterior and lateral thigh to knee level, and posterior, which pierces the fascia lata higher than the anterior ramus and divides to innervate the skin on the lateral surface of the thigh, from the greater trochanter to the middle of the thigh, with occasional extension to the gluteal skin.[5]

Finally, the obturator nerve is a sensorimotor nerve that arises from the anterior division of the 2nd to the 4th ventral lumbar ramus and supplies the medial compartment of the thigh, descends through the psoas major and emerges from the medial border at the pelvic border, crosses the posterior sacroiliac joint to the iliac vessels and runs along the lateral pelvic wall medial to the obturator innerum and anterosuperior to the obturator vessels.[5] Figure 4 highlights, in a video-assisted surgery drawing, the anatomy of the nerves.

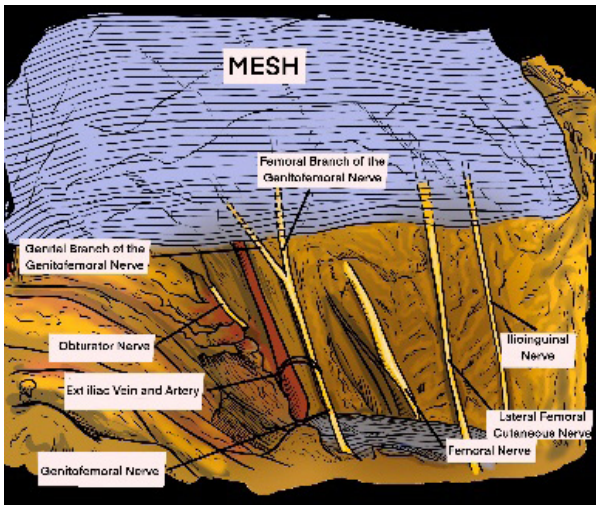


FIGURE 4 — Nerves of the inguinal region: anatomical schematic drawing of video-assisted operation

Surgical description: the TAPP and PTE approaches

TAPP (preperitoneal transabdominal approach) is a type of laparoscopic correction for hernias. This repair requires general anesthesia3 and the peritoneal incision is performed from the medial umbilical ligament, elliptically following the arch of the transverse muscle, extending to the anterosuperior iliac spine. The process can be performed from medial to lateral or lateral-to-medial. The dissection of the peritoneum and the preperitoneal space is complete when the component elements of the inverted Y are seen, as well as the iliopsoas, pubis, and pectineal ligament. Once properly dissected, the prosthesis is properly placed, so that it covers all areas of weakness in the inguinal region with an overlap of about 3-4 cm. Therefore, it is important to start the incision at least 4 cm above the deep edge of the inguinal ring, to allow the placement of the prosthesis, which should reach the pubic symphysis medially and the iliopsoas muscle laterally, and should also extend up to 2 cm below the pubis and cover at least 3 cm of the anterior abdominal wall in relation to the deep inguinal ring. Peritoneal closure should be done to cover the mesh and avoid its contact with the intraperitoneal structures. Another concern of the closure of the peritoneum is that it should not bend the lower portion of the mesh, a potential cause of hernia recurrence. The wide lower dissection of the peritoneum avoids this complication. It is important to note that the introduction of mesh reinforcement in inguinal hernia repair significantly reduces the recurrence rate, and the main clinical challenge is chronic pain.[9]

In the PTE approach (fully extraperitoneal laparoscopic technique), the peritoneal cavity is not penetrated and the mesh is used to seal the hernia from the outside of the peritoneum. It is important to be aware of the nerves when separating the hernial sac from the cord structures and when attaching the mesh, specifically when applying stitches to bring the mesh closer to the pubic tubercle and when attaching the inferior edge of the mesh to the inferior border of the inguinal ligament. The iliohypogastric nerve sits superior to the cord and ligament structures at groin dissection, and this structure should be identified by fixing the mesh superiorly.[8]

In laparoscopic repair, both this nerve and the ilioinguinal nerve have a lower risk of being injured. Meanwhile, the genital or femoral branches of the genitofemoral nerve may suffer injury in the open or laparoscopic preperitoneal space, either by thermal or electrical injury, by excessive dissection of the pain triangle (lateral to the inferior epigastric vessels, traction, entrapment or even injuries caused by sutures).[5]

Ways to solve and prevent inguinodynia

The European Hernia Society guidelines recommend the identification of the 3 inguinal nerves (ilioinguinal, iliohypogastric, and genital branch of the genitofemor) for the reduction of late postoperative pain due to nerve injuries,[6] which can be caused by intraoperative direct or indirect involvement secondary to mesh placement.[8] Knowledge of the anatomy of these nerves can thus facilitate their identification and proper management, reducing risks and significantly improving the safety

and success rate of surgical procedures, not only for inguinal hernia repair, but also for varicocele operations and ilioinguinal/iliohypogastric blocks with ultrasound-guided or landmark-based techniques.[6] Documentation of the presence or absence of innervation, and whether it was adequately protected during the procedure, provides evidence that the surgeon sought to identify it in order to avoid direct injury. Formal recording of nerve preservation or sacrifice may influence the future management of the patient if he or she develops inguinodynia. Without clear documentation, it is not possible to plan future therapeutic interventions if patients return with chronic postoperative pain in the groin area.[8]

In addition, studies have shown that the identification and management of inguinal nerves for inguinal hernia repair is deficient in current procedures, which suggests that inguinal nerves have not been considered a priority in patients undergoing surgery. This may be due to the lack of anatomical knowledge of the region on the part of surgeons who frequently perform these operations.[8] In this sense, in cases where it is not possible to prevent nerve injury, a method to reduce postoperative pain in patients undergoing laparoscopy is to fix a mesh with glue, which is used in areas where the mesh can fully adhere against another flat surface. Therefore, the best adhesion of the screen, and consequent its lower folding, can be achieved in the three-dimensional myopectineal hole with precast 3D screen.[3] Laparoscopic triple neurectomy or robotic neurectomy can also be used, which is considered a safe and effective technique in the treatment of refractory chronic inguinal pain.[4] However, it should be borne in mind that successful treatment usually requires surgical intervention, but that failure of an initial surgical attempt is not uncommon, occurring in up to 20% of patients.[7]

CONCLUSION

Surgeons' knowledge of the nervous anatomical region by laparoscopic surgery is capable of preventing inguinodynia. The identification, recognition, and preservation or dissection when necessary of the main nerves in the region prevents chronic groin pain. Therefore, it is understood that with the surgical techniques currently available for hernioplasty, added to the expertise of the professional who performs the procedure, the correction of inguinal hernia can be mostly effective and without sequelae of chronic pain.

Authors' contributions

Ana Júlia Ribas Sigwalt: Conceptualization, Writing (review and editing)
Marcos Fabiano Sigwalt: Formal analysis, Methodology, Writing (review and editing)
Lívia Dala Déa Ferreira Pocay: Investigation, Writing (review and editing)
Mahara Freitas dos Santos, Investigation, Writing (review and editing)
Tailla Cristina de Oliveira: Investigation, Writing (review and editing)
Leonardo Wanderloff Franco: Investigation, Writing (review and editing)
Fernando Issamu Tabushi: Writing (original draft), Writing (review and editing)

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BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e0003

Bariatric surgery as a factor of colorectal cancer prevention – an integrative review

A cirurgia bariátrica como um fator de prevenção ao câncer colorretal – uma revisão integrativa

Jorge Daher Scander Sielski[1], Juliany Bendas Beiro[1], Mirella Mantovani[1], Marcos Fabiano Sigwalt[1]

ABSTRACT

Introduction: The increasing levels of obesity around the world and its intimate relation with colorectal neoplasms invite introspection to a protective effect of bariatric surgery.

Objective: To review articles that clarify the protective effect of bariatric surgery in the development of colorectal neoplasms.

Method: Integrative review based on PubMed and BVS databases, with the following keywords according to the platform Decs: "bariatric surgery and colorectal neoplasms". The subsequent process applied filters including publications from the last 5 five years, in English and Portuguese, that were complete. After critical analysis studies were selected based on their relevance and correlation with the theme.

Results: 16 articles were compared based on the effects of bariatric surgery in the prevention of colorectal cancer, which included different techniques and the relation between the pathophysiology of metabolic syndrome and carcinogenesis of the cancer studied.

Conclusion: It was observed that bariatric surgery, despite the used technique, has protective effect in the development of colorectal cancer.

KEYWORDS: Bariatric surgery. Colorectal neoplasms. Obesity.

RESUMO

Introdução: O aumento dos índices de obesidade no mundo e a sua íntima relação com o câncer colorretal faz refletir se procedimentos bariátricos poderiam ter algum efeito protetor no desenvolvimento dessa neoplasia.

Objetivo: Realizar revisão que esclareça o efeito protetor da cirurgia bariátrica no desenvolvimento de câncer de colorretal.

Método: Revisão integrativa de acordo com a base de dados PubMed e BVS, com os seguintes descritores, de acordo com a plataforma Decs: "*bariatric surgery and colorectal neoplasms*" com filtros que incluíssem artigos dos últimos 5 anos em inglês e português, e que estivessem completos. A partir da leitura dos textos filtrados foram selecionados os estudos de acordo com relevância e maior relação com o tema.

Resultados: Dezesseis artigos foram selecionados, comparando-se os efeitos da cirurgia bariátrica na prevenção do câncer de colorretal, incluindo as diferenças técnicas das operações e a relação da fisiopatologia da síndrome metabólica com a carcinogênese do tipo de câncer estudado.

Conclusão: A cirurgia bariátrica, independente da técnica utilizada, tem efeito protetor no desenvolvimento de câncer de colorretal.

PALAVRAS-CHAVE: Cirurgia bariátrica. Câncer colorretal. Obesidade.

Central Message

In recent years, there has been an exponential increase in the incidence of obese people in the world, considering it one of the great challenges of public health. Obesity is associated with several diseases, including colorectal cancer, which represents the third most common cancer in the world. Bariatric surgery, in turn, is an alternative that helps in weighted weight loss and, in the long term, has proven benefits in reducing the risk of cancer.

Perspective

Bariatric surgery presents a protective factor in colorectal cancer; this is justified by the understanding of the pathophysiological relationship between metabolic syndrome and obesity, since after the surgical procedure, there is a reduction in tissue inflammation, epigenetic changes and other biochemical factors, which hinder the carcinogenic process. In addition, when comparing the sleeve and bypass techniques, both were similar in terms of their protective effect against cancer.

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Conflict of interest: None | Funding: None | Received: 07/010/2024 | Accepted: 09/12/2024 | Publication date: 11/02/2025 | Correspondence: marcossigwalt@yahoo.com.br | Associate Editor: Thelma Larocca Skare

How to cite:
Sielski JDS, Beiro JB, Mantovani M, Sigwalt MF. A cirurgia bariátrica como um fator de prevenção ao câncer colorretal – uma revisão integrativa. BioSCIENCE. 2025;83:e00003

INTRODUCTION

The prevalence of obesity continues to increase worldwide, being one of the biggest problems for public health today1. In 2016, approximately 40% of adults over 18 years of age were overweight and 13% of the world's population was obese. In addition, compared to previous years, the preponderance of obesity practically tripled between 1975 and 2016. The consequences of this metabolic disorder are diverse, such as hypertension, type 2 diabetes, dyslipidemia, cardiovascular diseases, kidney injury, osteoarthritis and various cancers.[2]

Among the possible malignant diseases that can affect the obese population is colorectal cancer (CRC). This is the third most frequent cancer in the world and the second leading cause of cancer-related death, with approximately 1.8 million new cases and 881,000 deaths in 2018, with an expected increase in its incidence of up to 60% by 2030. In cases of CRC, studies have suggested that obesity is associated with an increased risk of up to 70% in men, in which it was perceived that for every 5 kg/m2 increase[1,3] in BMI there was a 24% increase in risk.[3]

Because of this, the various recommendations for cancer prevention include weight loss. However, for those who cannot reach their target weight with diet and exercise alone, bariatric surgery is a way to achieve rapid weight loss. Currently, it is considered for patients with a body mass index (BMI) equal to or greater than 40 kg/m2 or for those with a BMI equal to or greater than 35 kg/m2 with comorbidities related to obesity4. Studies have shown a strong association between weight loss, achieved after bariatric surgery, and a decrease in the risk of solid organ cancer. However, studies on the effect of bariatric surgery on CRC risk are still conflicting.[5]

The objective of this study was to review the effect of bariatric surgery on CRC, analyzing whether there was really any difference in those patients undergoing this procedure and whether different bariatric surgery techniques have divergent impacts.

METHOD

This is an integrative review, carried out according to the 6 stages foreseen for its development. The filters used to select the sample included works published in the last 5 years, in English and Portuguese and full texts. The first was to define the guiding question: "Is bariatric surgery a factor for preventing colorectal cancer?". In the second, the search or sampling in the literature in the PubMed and VHL databases was determined, with the descriptors Decs: "Bariatric surgery and colorectal neoplasms". In the third, the inclusion and exclusion criteria were defined, which included studies that addressed the guiding question, adult patients who underwent bariatric surgery, along with the keywords; texts that addressed only the relationship between obesity and colorectal cancer and that brought purely clinical treatments, without weight loss operations. The fourth stage, in turn, was the critical analysis of the included studies, which after applying the filter resulted in 8 articles; in PubMed, there were also 8 articles. Thus, joining the VHL and PubMed platforms, a total of 16 articles were selected (Figure). Finally, the fifth and sixth stages were the interpretation and synthesis of the results, comparing the data collected.

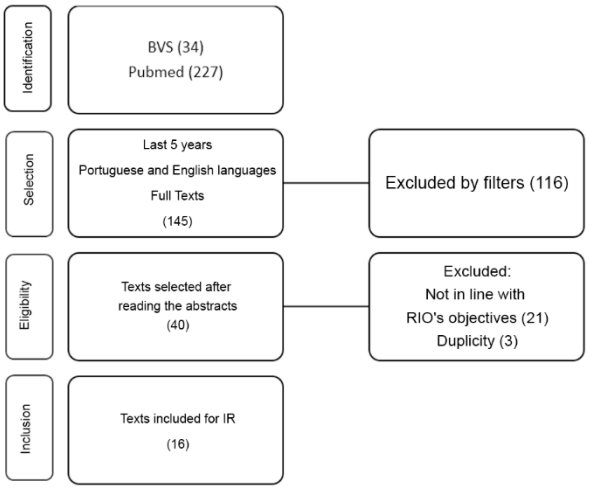

FIGURE — Summary of the methodology

RESULT

The Table shows the synthesis of the analysis of the articles focused on the theme in question.

DISCUSSION

The increase in the rates of obese and overweight patients is a public health concern. The high intake of industrialized and hypercaloric food leads to the accumulation of lipids, weight gain and consequently dysregulation of several biochemical reactions. Obesity is characterized by a state of low-grade systemic inflammation, which plays a significant role in the development of metabolic morbidity and, demonstrably, in the genesis of cancer.[2]

Excess adipose tissue in the body results in a state of inflammation due to oxidative stress, the spread of inflammatory cytokines, and increased DNA damage and repairs. The immune system is also impaired, as it results in dysbiosis, leading to even greater inflammation, contributing to cell mutation and consequently to the development of neoplastic cells.[3]

By 2016, almost 2 billion adults were obese and 650 million were overweight. In addition, about 481,000 new cases of cancer were diagnosed in adults aged 30 and older in 2012, presumably caused by increased body mass index (BMI).[2,6]

These obesity-related neoplasms mainly encompass colorectal cancer and other hormone-sensitive types, such as endometrial, breast, and prostate cancers. As for CRC, the magnitude of the risk associated with BMI is remarkable, being present in about 11.9% of obese men and 13.1% of obese women, and for each 5 kg/m2 increase in BMI, the risk of this cancer increases by 24% in

TABLE — Compilation of results based on their objectives

Number Reference	Title	Authors	Kind	Goals	Periodic
11	The protective effect of bariatric surgery on the development of colorectal cancer: A systematic review and meta-analysis	Nikolaos Pararas; Anastasia Pikouli; Dionysios Dellaportas; Constantinos Nastos; Anestis Charalampopoulos; Mohamad Ayham Muqresh; George Bagias; Emmanouil Pikoulis; Dimitrios Papaconstantinou	Meta-analysis	To investigate whether bariatric surgery reduces the risk of developing colorectal cancer in morbidly obese patients	International Journal of Environmental Research and Public Health Doi: 10.3390/ijerph20053981
22	Systematic review and meta-analysis of the impact of bariatric surgery on future cancer risk	Robert B. Wilson; Dhruvi Lathigara; Devesh Kaushal	Systematic review	To analyze whether bariatric surgery reduces cancer incidence and mortality, especially in types associated with obesity	International Journal of Molecular Sciences DOI: 10.3390/ijms24010447
33	Does bariatric surgery reduce the risk of colorectal cancer in individuals with morbid obesity? A systematic review and meta-analysis	Andrea Chierici; Paolo Amoretti; Céline Drai; Serena De Fatico; Jérôme Barriere; Luigi Schiavo; Antonio Iannelli	Systematic review	To investigate whether bariatric surgery reduces the incidence of colorectal cancer in patients with obesity by analyzing meta-analysis of 18 studies	MDPI DOI: 10.3390/nu15010087
44	Incidence of polyp formation following bariatric surgery	Andrew C. Droney; William Sellers; Anjuli Gupta; Kelly Rose Johnson; Marcus Fluck; Anthony Petrick; Joseph Bannon; Thomas Erchinger; Bogdan Protyniak	Integrative review	To investigate patients undergoing weight reduction surgery and their potential for developing precancerous lesions or polyps with carcinogenic potential, aiming to clarify any risk factors or relationships between bariatric surgery and colorectal cancer.	Surgery for Obesity and Related Diseases doi: 10.1016/j.soard.2021.06.020
55	Long-term incidence of colorectal cancer after bariatric surgery or usual care in the Swedish obese subjects	Magdalena Taube; Markku Peltonen; Kajsa Sjo¨holm; Richard Palmqvist; Johanna C. Andersson-Assarsson; Peter Jacobson; Per-Arne Svensson; Lena M. S. Carlsson	Original	To examine long-term incidence of colorectal cancer after bariatric surgery and usual care, based on intervention study of Swedish obese subjects (SOS)	Plos One DOI: 10.1371/journal.pone.0248559
66	Colorectal cancer risk following bariatric surgery in a nationwide study of french individuals with obesity	Laurent Bailly; Roxane Fabre; Christian Pradier; Antonio Iannelli	Cohort	To investigate whether bariatric surgery affects the risk of developing colorectal cancer in people who are overweight	JAMA Surgery Doi: 10.1001/jamasurg.2020.0082
77	Obesity surgery and risk of colorectal and other obesity-related cancers: an English population-based cohort study	Ariadni Aravani; Amy Downing; James D. Thomas; Jesper Lagergrenc; Eva J.A. Morris; Mark A. Hull	Cohort	To investigate whether bariatric surgery is associated with changes in cancer risk, including colorectal, breast, endometrial, kidney, and lung cancers, compared to obese patients without operations.	Cancer Epidemiology doi: 10.1016/j.canep.2018.01.010
88	Biomarkers of colorectal cancer risk decrease 6 months after Roux-en-Y gastric bypass surgery	Sorena Afshar; Fiona Malcomso; Seamus B. Kelly; Keith Seymour; Sean Woodcock; John C. Mathers	Cohort	To assess the impact of weight loss and bariatric surgery in relation to colorectal cancer	Obes Surg DOI: 10.1007/s11695-017-2972-3
99	The long-term impact of roux-en-y gastric bypass on colorectal polyp formation and relation to weight loss outcomes	Hisham Hussan; Alyssa Drosdak; Melissa Le Roux; Kishan Patel; Kyle Porter; Steven K. Clinton; Brian Focht; Sabrena Noria9	Integrative review	To assess the long-term impact of Roux-en-Y gastric bypass on precancerous colon polyps and to identify risk factors associated with this increased risk.	Obes Surg DOI: 10.1007/s11695-019-04196-3
1010	Colorectal cancer after bariatric surgery (Cric-Abs 2020): Sicob (Italian Society of Obesity Surgery) endorsed national survey	Maria Chiara Ciccioriccio; Angelo Iossa; Cristian Eugeniu Boru; Francesco De Angelis; Pietro Termine; Mary Giuffrè; Gianfranco Silecchia	Cohort	To analyze the incidence of colorectal cancer after bariatric surgery in Italy, comparing techniques to determine whether it is associated with the development of this type of cancer.	International Journal of Obesity DOI: 10.1038/s41366-021-00891-7
1111	Evaluating the correlation of bariatric surgery and the prevalence of cancers in obese patients: a study of the national inpatient sample (NIS) database	Devashish Desai, Sachi Singhal, Jean Koka	Cohort	To understand whether bariatric surgery can reduce the prevalence of certain cancers in morbidly obese patients.	Cureus Doi: 10.7759/cureus.23987
1212	Bariatric surgery is independently associated with a decrease in the development of colorectal lesions?	Minyoung Kwak; J. Hunter Mehaffey; Robert B. Hawkins; Traci L. Hedrick; Craig L. Slingluff Jr; Bruce Schirmer; Peter T. Hallowell; Charles M. Friel	Case-control	To review patients undergoing bariatric surgery, comparing with non-operated patients for demographics, comorbidities, body mass index, and socioeconomic factors	Surgery doi: 10.1016/j.surg.2019.04.015
1313	The impact of surgical weight loss procedures on the risk of metachronous colorectal neoplasia: the differential effect of surgery type, sex, and anatomic location	Hisham Hussan; Mohamed R. Ali; Shehnaz K. Hussain; Victoria Lyo; Eric McLaughli; ChienWei Chiang; Henry J. Thompson,	Cohort	To evaluate the impact of bariatric operations (sleeve gastrectomy and Roux-en-Y gastric bypass) on the risk of colorectal polyp recurrence in patients with a prior history of polyps, comparing them with controls without bariatric surgery	Journal of the National Cancer Institute Monographs DOI: 10.1093/jncimonographs/lgad009
1414	The impact of bariatric surgery on colorectal cancer risk	Sara D'Amato; Maria Sofia; Marcello Agosta; Giorgia Litrico; Iacopo Sarva; Gaetano La Greca; Saverio Latteri	Integrative review	Understanding whether bariatric surgery, especially Roux-en-Y gastric bypass, increases the risk of colorectal cancer and the mechanisms involved	Surgery for Obesity and Related Diseases doi: 10.1016/j.soard.2022.10.015
1515	Colon and rectal cancer risk after bariatric surgery in a multicountry Nordic cohort study	Wenjing Tao; Miia Artama; My von Euler-Chelpin; Mark Hull; Rickard Ljung; Elsebeth Lynge; Guðríður H. Ólafsdóttir; Eero Pukkala; Pål Romundsta; Mats Talbäck; Laufey Tryggvadottir; Jesper Lagergren	Cohort	To investigate whether bariatric surgery increases the risk of colorectal cancer in obese patients by looking at a group of adults over several decades in the Nordic countries.	International Journal of Cancer DOI: 10.1002/IJC.32803
1616	Bariatric surgery is associated with a recent temporal increase in colorectal cancer resections, most pronounced in adults below 50 years of age	Hisham Hussan; Arsheya Patel; Samuel Akinyeye; Kyle Porter; Dennis Ahnen; David Lieberman	Cohort	To investigate the incidence of colorectal cancer in relation to other obesity-related gastrointestinal cancers, among morbidly obese individuals who have undergone bariatric surgery and those who have not.	Obes Surg DOI: 10.1007/s11695-020-04921-y

men and 9% in women[7]. This important relationship is not only observed in malignant lesions, but also in premalignant lesions, such as colorectal adenoma.[8]

The pathophysiology involving the relationship between obesity and CRC can be explained by biochemical markers, with changes in the mechanisms that drive cancer, such as increased insulin sensitivity, decreased insulin-like growth factor-1 (IGF-1), decreased adiponectin, increased inflammation of adipose and systemic tissue, increased leptin, epigenetic changes, among others.[9,10]

Through these significant associations between obesity and colorectal cancer, it becomes crucial to promote healthy lifestyle habits. For the reduction of obesity, lifestyle changes are only responsible for the loss of 5-10% of the body mass of the obese individual. In addition, it is a method that is difficult to adhere to and sustain in the long term, mainly due to

the various complications that obesity brings, such as depression, nutritional deficiency, a state of constant inflammation, osteoarthritis and sarcopenia.[2]

Bariatric surgery, in turn, promotes consistent weight loss, resulting in a greater reduction of excessive adipose tissue and consequently of the hyperinflammatory state. With the performance of the operation, there is significant weight loss, associated with the improvement of comorbidities.[2,11] Because of this, the hypothesis of bariatric surgery as a possible protective action in cases of CRC has been raised.

In this scenario, the literature is controversial, some studies have shown that there is a significant decrease in CRC cases, however, others consider bariatric surgery as a risk factor. There are also studies that show differences between the techniques, with Roux-en-Y bypass being associated with the worst prognosis.

A review was carried out encompassing more than 6.[2] million patients who underwent bariatric surgery and underwent a 5-year follow-up.[1] In the analysis of this study, a 44% reduction in the incidence of RCC was observed in the 2 main surgical procedures, gastric sleeve (GS) and Roux-en-Y bypass (RYGB).[1] Reinforcing this relationship, the 2023 Chierici study showed a significant reduction of 54% comparing a sample of 12.[5] million patients followed over the period of 3 to 20 years3. In addition, smaller studies followed this same trend, showing a reduction of up to 38% and an incidence of CRC of 0.10% after a 10-year follow-up of bariatric surgery.[10,12]

There were articles that failed to conclude this same relationship; however, they showed that obese patients without bariatric surgery had a risk of CRC of more than 34% compared to the general population. Concomitant with these findings, a significant decrease in polyp recurrence was also evidenced by 30% after the operation.[13]

Regarding the type of bariatric procedure, OS and RYGB were the most common surgeries, in which most studies indicated no significant difference in the risk of developing CRC.[3,10] However, in a small number of studies, there was a more protective effect with the use of GS.[1,14]

Another important variable is the gender of the participants. In women, the operation seems to be more beneficial, with a significant reduction in cases of CRC; for men, the data are more heterogeneous, some articles suggest that there are no differences when compared to women, and others suggest less protection after the procedure, resulting in higher incidences of CRC in this group.[3,10,12]

On the other hand, some studies have shown an increased risk of CRC after surgery for obesity, and the mechanisms underlying this are still uncertain. One of the hypotheses would be regarding the cellular and molecular changes in the gastrointestinal tract after it, mainly using samples obtained from the rectum to justify this relationship.[15] There are also authors who indicate only RYGB as a risk factor for CRC, stating that there would be hyperproliferation and inflammation associated with changes in the intestinal microbiota that would be related to carcinogenesis in these cases.[14]

In view of this heterogeneity, the meta-analysis by Chierici et al.[3] of 2023, suggested follow-up time as a possible influencer on the results obtained - the longer the follow-up time, the higher the incidence of cancer. In addition, in the studies analyzed, odds ratios and risk ratios were used to measure the risk of colorectal cancer, this represents an important limitation, as studies that report time-dependent risk estimates cannot be effectively compared when the follow-up interval is different. For this, this article used the hazard ratio as a risk measure, which is independent of time and allows the identification of the risk of CRC after bariatric surgery. From this, with a more in-depth observation of the studies used and using this other indicator, a 19% reduction in the risk of CRC was found after bariatric surgery.[3]

However, it is also important to highlight the influence of multifactorial factors and the lifestyle of bariatric patients, since, despite weight reduction and some inflammatory factors, there are genetic and behavioral issues, such as smoking, alcoholism, diabetes, which interfere with and increase the incidence of CRC.[5] In addition, there is evidence of recurrence in 20% of patients with a BMI ≥ 35 kg/m2 after 10 years, so bariatric surgery alone does not completely exclude risk factors.[16] In addition, most studies that showed it as a risk factor used only the information collected in databases, which can lead to bias if not correctly considered.

CONCLUSION

The association of CRC carcinogenesis with obesity and metabolic syndrome is increasingly elucidated and described as an important modifiable risk factor. Knowing the great difficulties and limitations that the population encounters in weight loss, bariatric surgery has positive results both in weight loss and in reducing the incidence of related cancers. Even with a certain discrepancy in the results in the literature, it is perceived that in the most recent studies it is possible to conclude that there is a protective factor of the bariatric procedure, regardless of the technique (SG and RYGB), in the development of colorectal cancer, mainly due to the consequent biochemical changes, making them more physiological and less carcinogenic. It is necessary to note, however, that performing the procedure, without the proper criteria, does not have a strong impact on the prevention of colorectal cancer.

Authors' contributions
Jorge Daher Scander Sielski: Conceptualization
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Mirella Mantovani: Writing (original draft)
Marcos Fabiano Sigwalt: Writing (review and editing)

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BioSCIENCE Original Article
DOI: https://doi.org/10.55684/2025.83.e00004

Impact of using teleneurology on reducing referrals in the single health system

Impacto da utilização da teleneurologia na redução de encaminhamentos no sistema único de saúde

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ABSTRACT

Introduction: Telemedicine, when applied to neurology, allows for better diagnosis and more specific and appropriate procedures, as well as a highly economical outcome due to the reduction in unnecessary referrals.

Objectives: To analyze the impact of using teleneurology on reducing referrals in the Unified Health System (SUS) and verify the associated variables that impacted referrals.

Method: Documentary, quantitative, descriptive and cross-sectional research, which was carried out using information contained in a database, constructed from services included in a platform that provides teleneurology services in Brazil. Analysis was performed to examine the relationship between the binary dependent variable (emergency referral) and a set of five independent variables (age, sex, treatment unit, clinical history and tomography results).

Results: The study comprised 2,165 medical records of patients who required neurological care via telemedicine between April 2019 and October 2022. After analysis, it was observed that the logistic regression model was statistically significant ($p<0.05$) for the healthcare unit. treatment, clinical history and tomography results, indicating that these variables were related to the probability of emergency referral. When examining the estimated coefficients in the care units, the chance of being referred via emergency was 0.59 times greater when in hospital than in SAMU, that is, those in the hospital are 41.01% less likely to be referred via emergency. However, those in the UPA are 39.17% less likely to be referred via emergency than in the SAMU.

Conclusion: The innovative approach to care provided greater diagnostic efficiency and therapeutic guidance, resulting in substantial savings for the SUS.

KEYWORDS: Brazilian Unified Health System. Sus. Referrals. Telemedicine. Teleneurology.

Central message

Telemedicine, when applied to neurology, enables better diagnosis and more specific and appropriate conducts, as well as a very economical outcome due to the reduction of unnecessary referrals. Thus, analyzing the impact of the use of teleneurology on the reduction of SUS referrals and verifying the variables associated with them is opportune with a view to speeding up care, reducing unnecessary referrals and lowering the costs of neurological care as a whole.

Perspective

This study demonstrated that the use of teleneurology reduced the number of unnecessary referrals in the SUS. After analyzing the associated variables collected, statistical significance was found in the independent variables, i.e., treatment units, clinical history and CT scan results, concluding that they have an impact on the occurrence of emergency referral. The use of teleneurology is beneficial to patients, the health system and the economic expenditure on treatment.

RESUMO

Introdução: A telemedicina quando aplicada à neurologia, possibilita melhor diagnóstico e condutas mais específicas e adequadas, bem como desfecho com grande economicidade devido à diminuição de encaminhamentos desnecessários.

Objetivos: Analisar o impacto da utilização da teleneurologia na redução de encaminhamentos no Sistema Único de Saúde (SUS) e verificar as variáveis associadas que impactaram no encaminhamento.

Método: Pesquisa documental, quantitativa, descritiva e transversal, que foi realizada a partir da utilização de informações contidas em banco de dados, construído de atendimentos inclusos em plataforma que presta serviços de teleneurologia no Brasil. Foi efetuada análise para examinar a relação entre a variável dependente binária (encaminhamento via emergência) e um conjunto de cinco variáveis independentes (idade, sexo, unidade de tratamento, história clínica e resultado da tomografia).

Resultado: O estudo compreendeu 2.165 prontuários de pacientes que demandaram atendimento neurológico via telemedicina entre abril de 2019 e outubro de 2022. Após a análise, observou-se que o modelo de regressão logística foi estatisticamente significativo ($p<0,05$) para unidade de tratamento, história clínica e resultado da tomografia, indicando que essas variáveis estavam relacionadas à probabilidade de encaminhamento emergencial. Ao examinar os coeficientes estimados nas unidades de atendimento, a chance de ter encaminhamento via emergencial foi 0,59 vezes maior estando no hospital do que no SAMU, ou seja, quem está no hospital tem 41,01% menos chances de ser encaminhado via emergencial. Contudo, quem está na UPA tem 39,17% menos chances de ser encaminhado via emergencial do que no SAMU.

Conclusão: A abordagem inovadora de atendimento proporcionou maior eficiência diagnóstica e orientação terapêutica, resultando em economia substancial ao SUS.

PALAVRAS-CHAVE: Encaminhamentos. Sistema Único de Saúde. SUS. Telemedicina. Teleneurologia.

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Conflict of interest: None | Funding: Partly by the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) – Funding code 001 | Received: 13/09/2024 | Accepted: 21/01/2025 | Publication date: 11/02/2025 | Correspondence: rafaelafernandesgoncalves@gmail.com | Associate Editor: Gustavo Rassier Isolan

How to cite:
Gonçalves RF, Giovanini AF, do Nascimento GB, Isolan GR, Sigwalt M, Polanski JF, Ribas-Filho JM. Impacto da utilização da teleneurologia na redução de encaminhamentos no sistema único de saúde. BioSCIENCE. 2025;83:e00004

INTRODUCTION

The discussion about variations in the methods of care and referral of patients has been relevant for many years in the health area. This is due to the persistence of several issues and divergences related to both the excessive transfer of patients to more complex hospital institutions and the deficiencies in directing which individuals truly require this type of care.

The processes of care flows and clinical management have become progressively more challenging as population changes are established. Due to this situation, better attention to the form and availability of services offered becomes a priority.[1]

The advancement of technologies in patient care has significantly revolutionized the provision of health care. Several technological innovations have contributed to improving the efficiency, accuracy, and accessibility of health services, especially telemedicine. It emerges as a transformative innovation in the field of health care delivery, representing a significant advance in the form of care delivery. This modality of care is becoming increasingly important, offering a variety of benefits that transcend geographical and temporal borders. By delving deeper into the analysis of these benefits, it becomes evident that telemedicine not only facilitates access to healthcare but also promotes operational efficiency.[2]

The growing demand for specialized neurology services has generated significant challenges in terms of access and efficiency in the Unified Health System (SUS), especially considering the complexity of neurological diagnoses and the shortage of specialized professionals in some regions of the country. In this context, teleneurology is inserted as a strategic and innovative tool.[2,3]

Thus, the objectives of this study were to analyze the impact of the use of teleneurology on the reduction of referrals in the SUS and to verify the associated variables that impacted referrals.

METHOD

This study was approved by the Human Research Ethics Committee of the Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil CAAE: 65591122.4.0000.0103. The research was carried out based on the use of information contained in a database, built of services included in the CEANNE telemedicine platform, which provided teleneurology services in 21 units in Brazil to SUS users. The study comprised 2,165 medical records of patients who required neurological care via telemedicine between April 2019 and October 2022. The data were analyzed through descriptive statistics, through the description of absolute and relative frequencies for categorical variables and measures of relative trend and dispersion for numerical variables, in addition to univariate and multivariate statistical analysis. Ethical aspects were respected according to CNS Resolution No. 510/2016.

Sample selection and data collection

The database used was prepared using 2165 medical records of patients who were SUS users who required care neurological via telemedicine in the 21 Brazilian units where the service was offered. Data collection occurred anonymously, without identifying the patients, with their consent form for the study. All consultations had a series of mandatory information that had to be provided by the physician who was performing the care and some complementary data at the discretion of those who used the service.

Complete medical records were included with information on patients who used teleneurology as a form of care, and excluded those that were incomplete or inconclusive, which would make the statistical analysis unfeasible, and those that were not related to the teleneurology service.

Operation of the Ceanne telemedicine platform

In this study, care took place remotely, by a specialized medical team, available 24 hours a day, together with the local professional who performed the initial evaluation of the patient, thus ensuring qualified and adequate care in the 21 units included in the study (Table 1).

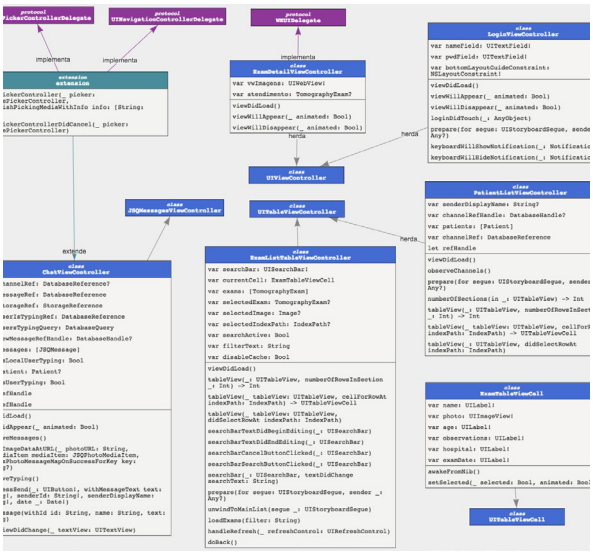
TABLE 1 — List of teleneurology care units included in the research

No.	Service Unit
1	Campo Belo
2	Canoas Psychosocial Care Center
3	Psychosocial Care Center Porto Alegre
4	Santa Terezinha de Erechim Hospital Foundation
5	University Foundation of Cardiology
6	São Vicente Charity Hospital
7	Santo Ângelo Charity Hospital
8	Hospital Regional de Santa Maria
9	Senhora Aparecida Hospital in Luz
10	IB Health
11	Manoel Gonçalves
12	SAMU Divinópolis
13	Santa Casa de Misericórdia São Vicente de Paulo
14	Santa Casa de Misericórdia de Santo Antônio do Monte
15	Divinópolis Basic Health Unit - Central Base
16	24-Hour Emergency Care Unit Father Roberto Cordeiro Martins
17	Antônio José dos Santos Emergency Care Unit
18	Nova Serrana Emergency Care Unit
19	Padre Roberto Emergency Care Unit
20	Rio Grande Emergency Care Unit
21	Lagoa da Prata Emergency Care Unit

The specialists evaluated each case by associating the interview data provided by the team with the tests provided by the local physician; in addition, the care relied on several protocols and diagrams provided by the system, always ensuring the necessary expertise for each case associated with the optimization of the communication channel between the remote specialist physician and the team present at the hospital of origin (Figures 1,2,3,4,5).

Source: Isolan et al.,2021[4]

FIGURE 1 — Class diagram of the Ceanne Médico application

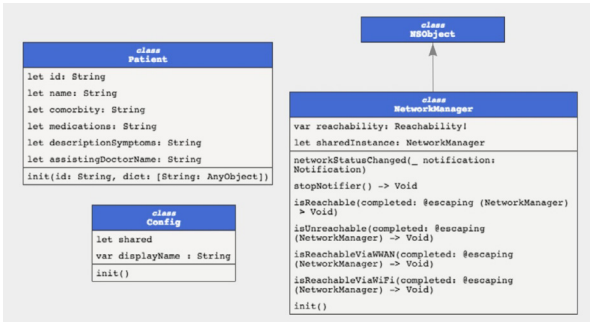


Source: Isolan et al.,2021[4]

FIGURE 2 — Class diagram of the Ceanne Médico application interface

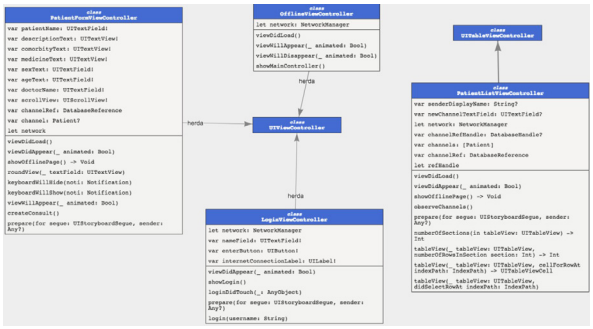
Source: Isolan et al.,2021[4]

FIGURE 3 — Access screen to the Ceanne Hospital system



Source: Isolan et al.,2021[4]

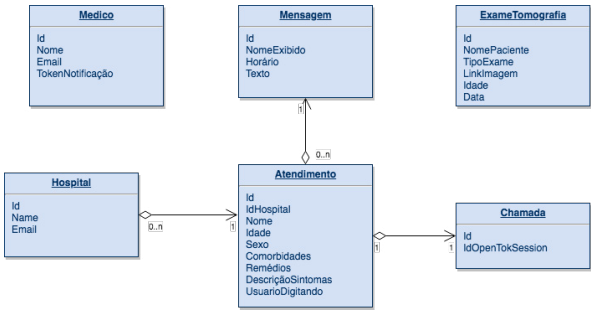
FIGURE 4 — Class diagram of the Ceanne Hospital application



Source: Isolan et al.,2021[4]

FIGURE 5 — Class diagram of the Ceanne Hospital application interface

The analysis of the cases occurred in an agile, safe and effective interphase, due to the use of a class diagram that provided interconnected processing of clinical and imaging data (Figures 6,7,8,9,10).



Source: Isolan et al.,2021[4]

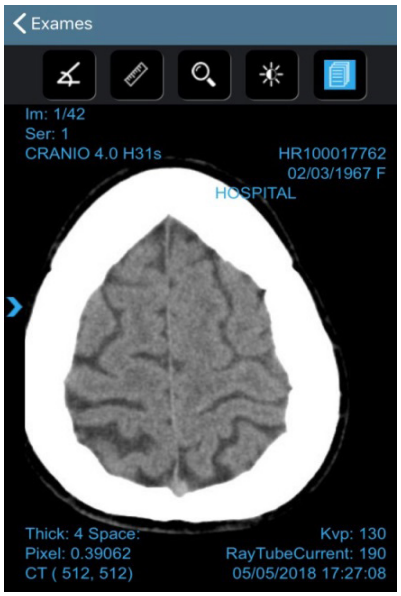
FIGURE 6 — Entity-relationship diagram of the Ceanne system database

Source: Isolan et al.,2021[4]

FIGURE 7 — Access screen to the Ceanne call center system

Source: Isolan et al.,2021[4]

FIGURE 8 — Screen for entering patient information for teleservice in the Ceanne application



Source: Isolan et al.,2021[4]

FIGURE 9 — Image of the tomography interface on the Ceanne teleservice platform

Source: Isolan et al.,2021[4]

FIGURE 10 — Illustrative screen of the list of exams performed by the patient connected to the Ceanne teleservice platform

Statistical analysis

The independent variables were age, gender, treatment unit, clinical history, and CT scan results, and were included in the analysis based on sample number and clinical importance. The dependent variable was emergency referral, being binary with yes or no answers. For the descriptive analysis of the qualitative variables, absolute and relative frequencies were used. Due to the qualitative nominal binary character of the dependent variable, a logistic regression model was used to determine whether there was a significant relationship between the independent variables and the probability of emergency referral. Before performing the logistic regression analysis, the assumptions of multicollinearity (VIF), presence of outliers, and linear logarithmic relationship between the continuous independent variables age and the dependent variable were verified. These checks ensured that the assumptions of logistic regression were met and that the results were reliable. The maximum likelihood method was used to estimate the regression coefficients and the respective confidence intervals. Based on the estimated coefficients, it was possible to obtain Odds Ratio (OR) associated with each category of the independent variables. In addition, the R^2Nagelkerke was used as an adjustment measure to evaluate the overall quality of the logistic regression model. It is an adaptation of the coefficient of determination R^2, originally used in linear regression models, for the context of logistic regression. All analyses were performed in Software R (R Core Team, 2022), with a significance level of 5%.

RESULT

This study presented a detailed analysis of the profile of neurological care via telemedicine of SUS users, focusing on the relationship between emergency referral and relevant variables. Tables 2,3,4 provide a comprehensive overview of the characteristics of the patients, the referral units, the observed tomographic alterations, and the factors associated with emergency referral.

TABLE 2 — Frequency table of the evaluated data profile

Variable	Absolute frequency	Relative frequency (%)
Sex		
Female	864	39,91
Male	1301	60,09
Service units		
Hospitals	285	13,16
SAMU	1139	52,61
UPA	741	34,23
Clinical history		
Headache	1121	51,78
Clinical complaint	129	5,96
Progressive neurological symptoms	290	13,39
Sudden neurological symptoms	165	7,62
TEC	448	20,69
TRAIN	12	0,55
CT scan result		
With amendment	1314	60,69
No change	851	39,31
Emergency referral		
Yes	684	31,59
No	1481	68,41

TABLE 3 — Table of frequency of tomographic alterations

Variable	Absolute frequency	Relative frequency (%)
Hemorrhagic stroke	234	10,81
Old ischemic stroke	139	6,42
New ischemic stroke	165	7,62
Skull subsidence fracture	3	0,14
Stable spine fracture	4	0,18
Osteodegenerative changes of the spine	2	0,09
Unstable spine fracture	8	0,37
Skull fracture	36	1,66
Hydrocephalus	50	2,31
Aneurysmal SAH	37	1,71
Traumatic SAH	36	1,66
Other	129	5,96
No change	800	36,95
TBI with multiple findings	89	4,11
TBI with extradural hematoma	32	1,48
TBI with acute subdural hematoma	77	3,56
TBI with chronic subdural hematoma	101	4,67
TBI with contusion	173	7,99
TCE for gunshot wound	2	0,09
Brain tumor	48	2,22
Total	2165	100

TABLE 4 — Frequency table of the evaluated data profile

Variable	Emergency referral	
	No	Yes
Sex		
Female	596 (27.53%)	268 (12.38%)
Male	885 (40.88%)	416 (19.21%)
Care unit		
SAMU	670 (30.95%)	469 (21.66%)
Hospitals	217 (10.02%)	68 (3.14%)
UPA	594 (27.44%)	147 (6.79%)
Clinical history		
Headache	846 (39.08%)	275 (12.70%)
Clinical complaint	85 (3.93%)	44 (2.03%)
Progressive neurological symptoms	145 (6.70%)	145 (6.70%)
Sudden neurological symptoms	135 (6.24%)	30 (1.39%)
TEC	268 (12.38%)	180 (8.31%)
TRAIN	2 (0.09%)	10 (0.46%)
CT scan result		
With amendment	714 (32.98%)	600 (27.71%)
No change	767 (35.43%)	84 (3.88%)

Logistic regression analysis was performed to examine the relationship between the binary dependent variable (emergency referral) and a set of 5 independent variables (age, gender, treatment unit, clinical history, and CT scan results). The objective was to determine whether the independent variables (factors) were associated with the probability of occurrence of emergency referral.

After the analysis, it was observed that the logistic regression model was statistically significant ($p<0.05$) for some categories of the independent variables: treatment unit, clinical history, and CT scan results (Table 5), indicating that these independent variables were related to the probability of occurrence of emergency referral. By examining the estimated coefficients, the Odds Ratios (ORs) for each category were calculated in relation to the reference category.

TABLE 5 — Results of multiple logistic regression regarding emergency referral in relation to the significant factors included in the model

Variable	β (EP)	P-value	OR (95% CI)
Age			
Age	-0.01 (0.01)	0.07	-
Sex			
Female (reference)	-	-	-
Male	-0.11 (0.24)	0.32	-
Care unit			
SAMU (reference)			
Hospitals	-0.53 (0.16)	0.001	0.59 (0.43-0.81)
UPA	-0.50 (0.12)	0.001	0.61 (0.48-0.78)
Clinical history			
Headache (reference)	-	-	-
Clinical complaint	-0.85 (0.22)	0.001	0.43 (0.28-0.66)
Progressive neurological symptoms	-0.26 (0.17)	0.12	-
Sudden neurological symptoms	-1.63 (0.23)	0.001	0.20 (0.12-0.31)
TEC	-0.74 (0.15)	0.001	0.48 (0.36-0.64)
TRAIN	1.17 (0.78)	0.14	-
CT scan result			
With modification (reference)	-	-	-
No change	-2.41 (0.16)	0.001	0.09 (0.07-0.12)

EP=standard error; CI 95%=95% confidence interval; OR=odds ratio

In the care units, the chance of having been referred via emergency was 0.59 times higher when in the hospital than in the SAMU. In other words, those who were in the hospital were 41.01% less likely to be referred via emergency than those treated by SAMU. In turn, those who were in the UPA would be 39.17% less likely to be referred via emergency than those treated at SAMU. The relationship between hospital and UPA was not significant.

When analyzing the frequency of tomographic alterations, other CT scans that had artifacts or conditions of low incidence were included, for a better analysis of the statistical coefficients. Considering the CT scan result factor, the chance of having been referred via emergency was 91.03% lower among those who did not have CT abnormalities than among patients with CT.

In the clinical history , isolated reports of malaise, weakness and fatigue were grouped under the item clinical complaints, after analysis and medical evaluation that primary neurological causes for the symptoms were ruled out and to facilitate statistical analysis. In clinical history, headache complaints stood out as the highest proportion of emergency referrals. Clinical complaints, neurological symptoms, and TBI were, respectively, 57.47%, 80.48%, and 52.31% lower in emergency room referral compared to headache.

DISCUSSION

Historically, telemedicine began in 1970 in Boston, in the United States of America, with the purpose of serving rural areas. Since then, it has been used as an assistance tool for regions lacking specialists.[5]

Telemedicine, as defined by the World Health Organization, refers to the provision of health services by professionals who make use of information and communication technologies. These tools are not only

limited to the validation of diagnoses, treatments, and preventive measures, but also extend to research and the provision of continuing education, training professionals for this purpose.[6]

Regarding the implementation of remote care, the studies identified several facilitating factors and barriers to the use of telemedicine in clinical practice. The facilitators included the support of managers, professionals and patients, the availability and adequacy of technological resources, the integration with existing systems, and the capacity building and training of those involved. Barriers included resistance to changing the form of care, lack of financial incentives, legal and ethical issues, usability and reliability of equipment, and technical and organizational challenges.[7]

Based on the remote care modality, it was possible to provide health services at a distance that could involve in an integrated way not only teleconsultations, but also teleeducation of the user.[2]

From the teleservice, it was also possible to offer users who had difficulty in accessing evaluation by specialists and greater complexity of care. In addition, the use of telemedicine was safe for the outpatient follow-up of some patients, especially in the postoperative period or who had difficulty moving, as occurred in the coronavirus pandemic, or also for those with low purchasing power.[8]

The scientifically proven advantages of teleconsultation were diverse, including the reduction of the need for patient travel, facilitated access to specialized care, reduction of the burden on the patient and caregiver, improved patient satisfaction, better family engagement in the care process, and reduced costs to the health system.[9]

According to the Ontario Telemedicine Network (OTN), a Canadian global platform for tracking, technology and data management via telemedicine, it has saved around US$ 1.3 billion in healthcare costs per year since the beginning of the use of teleservice. According to Canada Health Infoway, 77% of Canadian physicians reported using some type of digital health technology in 2018, up 14% from 2016. A 2017 Accenture report reported that telemedicine could save up to $10 billion in healthcare costs in the United States. OTN also reported that virtual visits can save up to 4 hours of travel time for patients living in rural areas.[10]

Corroborating this, other studies have historically proven the cost reduction to health services with the use of remote care. Telemedicine can reduce healthcare costs by up to 20% by reducing hospital admissions, patient transfers, face-to-face consultations, and unnecessary tests. Telemedicine can increase patients' quality of life by up to 30% by improving access to services, reducing waiting times, avoiding commuting, and facilitating follow-up. Teleconsultation has also increased the accuracy of the diagnosis of neurological diseases by up to 40% by allowing the evaluation of specialists at a distance, has proven better adherence to the treatment of neurological diseases by up to 50% by offering continuous support and guidance to patients, increased satisfaction with health services by up to 70% by providing greater autonomy and participation in therapeutic decisions, as well as the satisfaction of health professionals with their work by up to 80% by facilitating communication, collaboration and continuing education.[11]

Regarding clinical effectiveness, several studies have found that telemedicine was at least as effective as face-to-face care, and some have shown that it improved the clinical outcomes of patients, especially when comparing data from neurological diseases requiring brief intervention, as in the case of stroke.[7]

Current evidence indicates that telemedicine was an indispensable tool used as a complement to face-to-face consultations in various areas of neurology and the expansion of technological resources developed together. The coronavirus pandemic has notably intensified this process.

Different modalities of telemedicine in the various areas of neurology were studied, including teleconsultation, teleconsulting, telerehabilitation, telemonitoring and teleeducation. The advances achieved by teleneurology in this period stimulated technological innovations and health processes that created opportunities to improve the care provided to patients treated through this system.[2]

Teleneurology is of great importance to counteract the unequal dispersion of the number of neurologists per inhabitant in the various centers around the world.[6]

The importance of telemedicine care for the care of neurological diseases has already been well established in the literature. Remarkable progress in information and communication technologies has been witnessed, and telemedicine has emerged as a tool to expand access to medical care for different age groups, especially the elderly, overcoming physical and geographical obstacles.[12]

In this study, the results revealed that the average age of those treated via telemedicine was 55.52±22.63, with a minimum of 0 and a maximum of 109 years, which allowed us to conclude that all age groups were well represented in the study and that their analyses could be inferred regardless of age.

Study conducted between April 2020 and March 2021, in which [1]5,548 users were assisted via telemedicine, 64% were women (9,953) and 36% were men (5,595).[13] On the other hand, in this study, when analyzing the data in terms of gender, there was a predominance of men (60.09%).

In general, the care units had a great impact on the referral of emergency cases. Patients admitted to small/medium-sized hospitals had a higher probability of death, regardless of the time of arrival, especially due to the difficulty of brief specialized evaluation.[14]

In agreement with the above, this study demonstrated that the distribution of patients among the different care units was remarkable, with SAMU representing the largest proportion (52.61%) and the logistic regression analysis highlighted a significant association between emergency referral and hospital

units and UPA, indicating the influence of the care unit in relation to patient referral.

This analysis raised relevant questions about the growing role of telemedicine in the initial triage of these cases. Given the predominance of referral of patients who were primarily cared for by SAMU and the often urgent nature of neurological conditions, the effective integration of telemedicine in these units can accelerate diagnoses and optimize emergency referral.

The patient's clinical history, as an essential component of medical practice, has taken on a critical role in the emerging era of telemedicine. This modality of health care transformed the way health professionals interacted with patients, and consequently, raised fundamental questions about how telemedicine was essential for the evaluation of patients with an individual clinical history of atypical chronic headache, for example, who were on some occasions unequivocally referred to specialized evaluation.[15]

Headache has a high prevalence globally and relevance in the context of emergency care, being among the 10 most prevalent causes in the world and one of the 5 years lived with disability.[16]

In this context, headache stood out among the emergency complaints, as a prevalent symptom in both severe and common cases in medical practice, reiterating the importance of accurate diagnosis and brief referral in the case of acute cause.[17]

According to this series, headache stood out as the most evidenced report after analyzing the proportion of emergency referrals. Clinical complaints, sudden neurological symptoms, and TBI were, respectively, 57.47%, 80.48% and 52.31% lower in the emergency room referral item in relation to headache.

The efficacy of telemedicine and teleradiology, compared to telephone consultations, was evaluated through prospective, randomized, blinded clinical trials, known as STRokE DOC (STRokE DOC and STRokE DOC-AZ TIME). Together with other studies, this analysis confirmed that the remote evaluation of cranial CTs for decision-making on rt-PA treatment in cases of acute stroke, by means of telemedicine, was a reliable method. This study contributed significantly to the validation and implementation of these telecare modalities in clinical practice, highlighting the importance of remote assessment for the effectiveness of treatment in critical situations such as acute stroke.[18]

In addition, the use of teleradiology stood out as an effective mechanism that avoided unnecessary referrals to specialists, allowing evaluations of radiological exams, such as CTs, by neurosurgeons or neurologists in hospitals that did not have these services in person. Results of a study focused on the pattern of transfer of patients with head trauma from a type II trauma center, without neurosurgery services, to a hospital that works with this type of care showed that consultations with neurosurgeons using teleradiology was a viable alternative in the management of patients with head trauma, since only 4% of the patients – initially hospitalized in the level II trauma center and not later indicated for referral to hospitals with specialized services – have evolved negatively and needed late transfer.[19]

Therefore, the analysis of brain CT changes became valuable, as they denoted statistical relevance in increasing the probability of emergency referral. Considering the CT scan result factor, the chance of being referred via emergency in this study was 91.03% lower among those who did not present CT changes compared to those with it.

Based on the above, it has traditionally become essential to analyze the pattern of patients with neurological diseases treated via telemedicine and referred to specialized centers, since it was observed excessive transfer of individuals to hospitals of greater complexity, as well as failures in these referrals because many of these patients did not need care in a specialized center, thus unnecessarily burdening the unified health system. The processes of diagnosis and clinical management have become progressively more challenging as population changes are established, and consequently, an increase in morbidity and mortality rates, which has become indispensable for the accurate diagnosis and referral of acute diseases, such as neurological diseases.

In summary, this study analyzed the number of SUS patients with neurological diseases treated via telemedicine and the impact of its use on the reduction of referrals via SUS, as well as the associated variables (age, gender, care unit, clinical history, and CT scan results).

Regarding the independent variables - treatment units, clinical history and CT scan results - it was concluded that the logistic regression model was statistically significant, indicating a relationship between them and the probability of occurrence of emergency referral. Analyzing the estimated coefficients, the ORs for each category were calculated in relation to the reference category, since OR is a measure of the change in the odds ratio of the occurrence of the emergency referral event associated with the given category, in comparison with the reference category. It is important to note that an OR greater than 1 indicates a positive association between the independent variable and the occurrence of the emergency referral event, while an OR greater than 1 indicates a negative association. In addition, it is important to consider the confidence intervals associated with the OR. Confidence intervals provide range of values within which the true OR is likely to be contained.

In general, the logistic regression model provided good adequacy to the data (R^2Nagelkerke=0.26), indicating that it was able to explain part of the variability in the occurrence of the event of emergency referrals. However, it is important to emphasize that logistic regression does not provide information on causality, only on the association between variables.

This study did not have a control group for two reasons: the first was the originality of teleneuroregulation by specialists and, therefore, it was not possible to have an objective and comparative historical measure of referrals by non-specialists; What is observed in

practice is that most patients with alterations in their CT scans are referred to neurologists/neurosurgeons in medium and high complexity reference units. The second was that there would be an ethical bias if we divided our sample into two groups, with and without teleneuroregulation, because we could not fail to offer neurological teleconsulting on purpose (control group) with it available to the patient.

CONCLUSION

This study demonstrated that the use of teleneurology reduced the number of unnecessary referrals in the SUS. After analyzing the associated variables collected, statistical significance was found in the independent variables, i.e., treatment units, clinical history and CT results, concluding that they have an impact on the occurrence of emergency referrals.

Authors' contributions

Rafaela Fernandes Gonçalves: Conceptualization
Guilherme Batista do Nascimento: Investigation
Allan Fernando Giovanini: Methodology, Writing (review and editing)
Jurandir Marcondes Ribas Filho: Methodology
Gustavo Rassier Isolan: Project administration, Writing (original draft)
José Fernando Polanski: Writing (original draft)
Marcos Sigwalt: Writing (review and editing)

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BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e00005

Necrotizing enterocolitis: a challenge in medical approach

Enterocolite necrosante: desafio na conduta médica

Wilma Lilia de Castro e Souza Silva[1], Luiz Martins Collaço[1]

ABSTRACT

Introduction: Necrotizing enterocolitis is a multifactorial condition that mainly affects premature newborns. In these newborns, the gastrointestinal system is not yet fully developed, which compromises the ability to defend against microorganisms and makes the intestine more susceptible to lesions. Premature newborns have a less developed immune system, making it difficult to fight infections and increasing vulnerability to intense inflammatory processes. These factors, together, create an environment conducive to inflammation and necrosis of the intestinal wall, leading to the disease.

Objective: To better understand the risk factors, their management, prevention and prognosis, reducing the risk of long-term sequelae.

Method: Integrative review with synthesis of evidence. The databases chosen were Pubmed, Scielo, Scopus and Lilacs using the descriptors: "newborn, prematurity, necrotizing enterocolitis AND or OR and their respective terms in English.

Result: The searches identified 13 studies that met the search strategy and were read in full, with their key points included in this review.

Conclusion: The disease affects premature babies, with the occurrence being higher the greater the prematurity. Low birth weight is also a predisposing factor, and the lower the weight, the greater the number of cases. Apgar below 7 in the 5th min of life and hypoxia during resuscitation may induce its presence. The initial complementary diagnosis should be made by simple radiography and abdominal ultrasound. Additionally, transfontanelle ultrasound should be used when hypoxic brain injury is suspected and echocardiogram when cardiac malformations causing intestinal hypoperfusion may be present.

KEYWORDS: Newborn. Prematurity. Necrotizing enterocolitis.

RESUMO

Introdução: Enterocolite necrosante é condição multifatorial que afeta principalmente recém-nascidos prematuros. Neles, o sistema gastrointestinal ainda não está completamente desenvolvido, o que compromete a capacidade de defesa contra microrganismos e torna o intestino mais suscetível às lesões. Recém-nascidos prematuros têm sistema imunológico menos desenvolvido, dificultando o combate às infecções e aumentando a vulnerabilidade a processos inflamatórios intensos. Esses fatores, em conjunto, criam ambiente propício para a inflamação e necrose da parede intestinal, levando ao quadro da doença.

Objetivo: Compreender melhor os fatores de risco, seu manejo, prevenção e prognóstico, diminuindo os riscos de sequelas em longo prazo.

Método: Revisão integrativa com síntese de evidências. As bases escolhidas foram Pubmed, SciELO, Scopus e Lilacs utilizando os descritores: "recém-nascido, prematuridade, enterocolite necrosante AND ou OR e seus respectivos termos em inglês.

Resultado: As buscas identificaram 13 trabalhos que atenderam à estratégia de busca e foram integralmente lidos, com seus pontos-chave incluídos nesta revisão.

Conclusão: A doença acomete bebês prematuros, sendo maior a ocorrência quanto maior a prematuridade. O baixo peso ao nascer também é fator predisponente, e quanto menor o peso, maior o número de casos. Apgar abaixo de 7 no 5º. min de vida e hipóxia durante reanimação podem ser indutores de sua presença. O diagnóstico complementar inicial deve ser feito por radiografia simples e ecografia abdominais. Adicionalmente, ecografia transfontanela deve ser utilizada quando se suspeita de lesão hipóxica cerebral e ecocardiograma na verificação de malformações cardíacas que acarretem hipoperfusão intestinal.

PALAVRAS-CHAVE: Recém-nascido. Prematuridade. Enterocolite necrosante.

Central message

The study and knowledge of necrotizing enterocolitis is relevant in the hospital environment due to the high mortality among patients affected by it, which brings a very high emotional cost to families. There is an increase in the length of stay in the neonatal ICU, and sequelae in the short and long term. Due to the limited existence of articles in the literature on the subject, this study sought to update the most important aspects in the approach to this serious disease.

Perspective

This review sought to add an update on the subject in order to better understand it, which is severe and requires rapid diagnosis for the installation of appropriate therapy. Analyzing the correlation of necrotizing enterocolitis with prematurity, low birth weight, hypoxia, and difference in the number of cases between sexes is important in the prognosis, as the measures to be taken must take into account the most efficient means and methods for diagnosis.

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Conflict of interest: None | Funding: Partly by the Coordination for the Improvement of Higher Education Personnel - Brazil (CAPES) – Funding code 001 | Received: 09/11/2024 | Accepted: 21/01/2025 | Publication date: 11/02/2025 | Correspondence: wilma.lilia@hotmail.com | Associate Editor: Ronaldo Mafia Cuenca

How to cite:
Gonçalves RF, Giovanini AF, do Nascimento GB, Isolan GR, Sigwalt M, Polanski JF, Ribas-Filho JM. Impacto da utilização da teleneurologia na redução de encaminhamentos no sistema único de saúde. BioSCIENCE. 2025;83:e00005

INTRODUCTION

Necrotizing enterocolitis (NEC) is a multifactorial condition, that is, it results from the combination of several factors that mainly affect premature newborns. In them, the gastrointestinal system is not yet fully developed, which compromises the ability to defend against microorganisms and makes the intestine more susceptible to injuries. In situations of imbalance in the intestinal microbiota, harmful bacteria can proliferate and generate inflammation, causing damage to the intestinal wall and promoting a lack of oxygen or reduced blood flow to the intestine, compromising the integrity of intestinal cells, and predisposing the tissue to necrosis. Early introduction of tube feeding (especially with artificial formula) may increase the risk of NEC as breast milk contains protective factors that reduce inflammation and promote healthy gut development. Premature newborns have a less developed immune system, making it difficult to fight infections and increasing vulnerability to intense inflammatory processes. These factors, together, create an environment conducive to inflammation and necrosis of the intestinal wall, leading to NEC. Knowledge of it is essential for health professionals and parents, as it enables early recognition of symptoms and rapid initiation of treatment. Studies show that rapid diagnosis and treatment are associated with lower rates of complications and mortality.

Thus, a better understanding of risk factors and their management can help in prevention and prognosis, reducing the risks of long-term sequelae. This is the objective of this review, which was to promote updating on concepts, diagnostic means and conducts.

METHOD

This is an integrative literature review with a synthesis of evidence. The databases chosen for the selection of the studies were Pubmed, SciELO, Scopus and Lilacs using the descriptors: "newborn, prematurity, necrotizing enterocolitis AND or OR,. Any work that discussed the proposed theme was initially included in the sample. After reading the titles and abstracts, those that did not adequately address the theme were excluded. The searches identified 13 papers that met the search strategy and were read in full, with their key points included in this review.

DISCUSSION

Pathophysiology

Necrotizing enterocolitis is a disease that affects the gastrointestinal tract of newborns, especially premature infants, who may have suffered hypoxia at birth or after. It is not uncommon for the clinical practice to be nonspecific, as well as the findings in complementary tests, which does not collaborate with diagnostic accuracy.[1]

Among its causative factors is the lesion of the intestinal mucosa, caused mainly by peri- or intrapartum hypoxia, evidenced by Apgar below 7 in the first minute. Apgar is a test that evaluates the health of the newborn in the first minutes of life, and observes 5 aspects of the baby's vitality. An Apgar score below 7 in the first minute of life indicates that the baby has suffered oxygen deprivation, which can have repercussions throughout life. Hypoxia also occurs due to congenital cardiac or intestinal malformation with low blood flow, which favors increased intestinal permeability, leading to mucosal lesions, subsequent necrosis and perforation.[1,2] Hypoxia may be due to complications of prematurity, such as hyaline membrane. Most premature infants receive exogenous surfactant to make up for production failure due to lung immaturity, and thus allow better gas exchange. Tissue hypoxia due to anemia is common in premature newborns, caused by hematopoiesis deficiency due to immaturity of the body, cerebral or pulmonary hemorrhage, and fragility of the body in formation. Consecutive blood collections, carried out to monitor the evolution, such as blood gases, blood count, blood culture, among others, are reasons for blood loss, and sometimes blood component transfusions are necessary.[3]

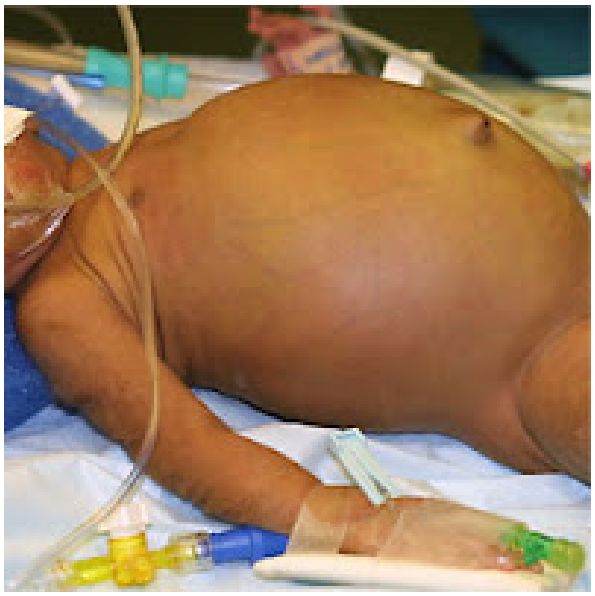
The presence of pathogenic bacteria is another factor that contributes to the occurrence of NEC. Microbial dysbiosis occurs due to inadequate colonization of the gastrointestinal tract of the newborn admitted to the neonatal ICU soon after birth, due to the use of antibiotic therapy, due to maternal complications in labor and premature rupture of membranes, vaginal colonization of the mother by group B streptococcal bacteria, or surgical delivery. The late start of feeding favors bacterial translocation, contributing to the performance of these microorganisms in the occurrence of the disease.[1]

Another factor is the metabolic substrate. Colostrum or fresh breast milk or pasteurized human milk provided to the baby will serve as nutrition for the microorganisms already present, or it can act as an aggressive factor to the intestinal mucosa that has already suffered injury by hypoxia. The use of infant formula instead of colostrum, breast milk or pasteurized human milk increases susceptibility to bacterial invasion, due to the risk of triggering an allergic response to cow's milk protein and causing aggression to the integrity of the intestinal mucosal barrier, in addition to the absence of protective substances in human milk that are not present in infant formula.[4]

Prematurity, a reality of many babies who have NEC, is accompanied by the immaturity of the gastrointestinal tract, known as dysmotility of the premature infant's intestine, allowing greater permeability of the organ's epithelium, aggravated by the decrease in the mucin barrier that works to protect the intestine, and low levels of immunoglobulins leading to reduced immunity. This probably explains why most cases occur in premature newborns: and in the literature, 90% of newborns operated on for this diagnosis have a gestational age of less than 37 weeks.[2]

Signs and symptoms

The newborn may initially present systemic clinical symptoms such as pallor, tachycardia, tachypnea, fever, hypoactivity, apnea, hypotension, bradycardia, impaired perfusion, and thermal lability. Frequent gastrointestinal signs are abdominal distension, food intolerance, increased gastric residue, bilious vomiting, presence of blood in the stool, relief of loops, and pain on abdominal palpation, which will have repercussions on changes in laboratory and imaging tests. Alterations of the abdominal wall, such as erythema, edema, mowering, and pallor, suggest the diagnosis, but are only observed in 10% of patients.[5]



Source: Prematurity.com[6]

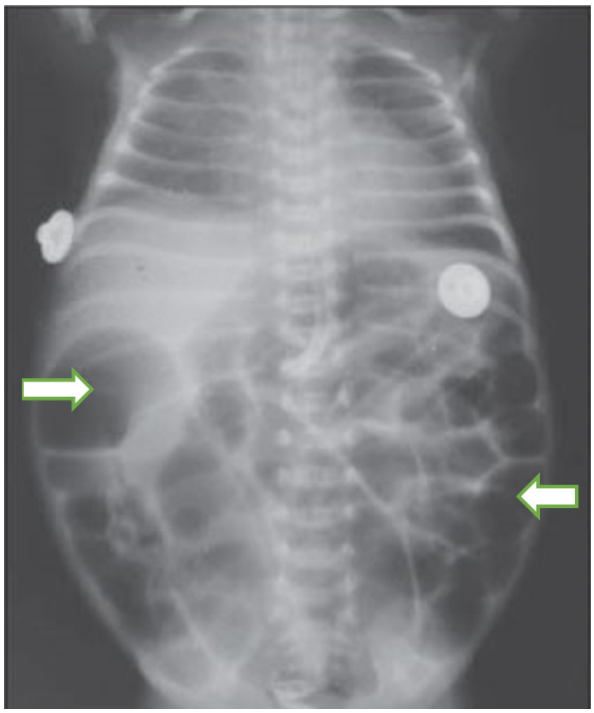
FIGURE 1 — Abdominal distension in a newborn with necrotizing enterocolitis

Diagnosis

Diagnosis is made considering the initial clinical manifestations such as food intolerance, increased gastric residue, abdominal distension, bilious vomiting, presence of blood in the feces (Figure 1).[5,7]

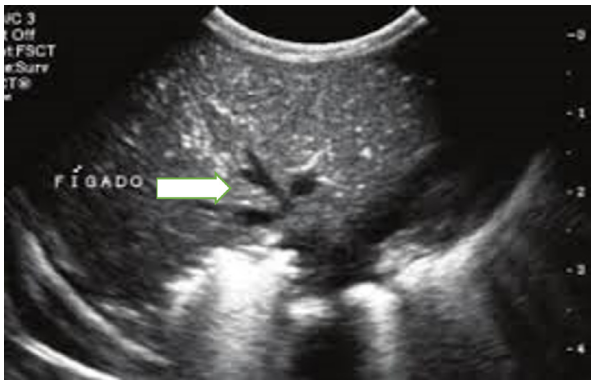
Laboratory findings serve as diagnostic aids but are not specific to NEC. These are leukopenia, thrombocytopenia, hyponatremia, hypokalemia, increased levels of C-reactive protein, instability of blood glucose, alteration of coagulation tests, and mixed acidosis. Radiological findings are dilated bowel loops, little gas in the intestine, fixed loops, which are intestinal loops distended with gas that do not change on serial radiographs (Figure 2). Pathognomonic findings on abdominal radiography are intestinal pneumatosis, air in the portal venous system, and pneumoperitoneum, which is a sign of intestinal perforation.[4,8]

Abdominal ultrasound may suggest the presence of abdominal fluid, thickening of the abdominal wall, decreased perfusion of the intestinal wall, which can be visualized early,[10] it is also possible to observe air in the portal system (Figure 3) and intestinal pneumatosis. In a study evaluating postoperative outcomes, the location of intestinal injury and subsequent perforation is more common in the ileum in preterm infants, and in extremely preterm infants in the jejunum.[2]



Source: Alvares et al.[9]

FIGURE 2 — Radiographic image of distended loops (arrows) suggestive of necrotizing enterocolitis



Source: Miranda et al.[12]

FIGURE 3 — Abdominal ultrasound showing air in the portal system

The clinical signs associated with the findings in imaging exams, abdominal X-ray or abdominal ultrasound, help in the classification of the so-called Bell Classification, and direct the treatment. It is divided into stages based on suspicion; signs and symptoms are added to the picture, contributing to locate it in the staging of the Bell et al classification. In 1978, these authors proposed the criteria classifying the disease into stages in order to guide therapeutic decisions. Subsequently, other authors[1,11] modified this criterion, including systemic, intestinal and radiographic signs (Table).

Auxiliary diagnostic tests

Most hospitals use radiographic anteroposterior study of the abdomen, lateral and supine position with serial horizontal rays for diagnosis and follow-up of the evolution of abominal conditions. The image obtained

TABLE — BELL staging modified by Walsh and Kleigman

Internship	Systemic signs	Intestinal signs	Picture Signs	Treatment
WOULD Suspicion ECN	thermal instability apnea, bradycardia, lethargy.	gastric residue, abdominal distension, vomiting, occult blood +	normal or with mild distension	Swim orally, antibiotics for 3 days, dependent on cultures
IB Suspicion ECN	thermal instability apnea, bradycardia, lethargy.	gastric residue, abdominal distension, vomiting, blood in the stool, enterorrhagia or melena.	normal or with mild distension	Swim orally, antibiotics for 3 days, dependent on cultures
IIA BCE set mildly ill	thermal instability, apnea, bradycardia, lethargy.	Same as above plus decreased or absent abdominal noises, with or without abdominal pain	Intestinal dilatation, ileus, intestinal pneumatosis	Nothing by mouth, antibiotics for 7-10 days, if the test is normal in 24-48 hours
IIB ECN Defined Moderately ill	As above, more mild metabolic acidosis and thrombocytopenia	Same as above, plus definite abdominal pain with or without abdominal cellulitis or mass in the right lower quadrant, absent bowel noises	Same as IIA, plus air in the portal vein, with or without ascites	Nothing by mouth, antibiotics for 14 days, correction of acidosis
IIIA ECN advanced. Seriously ill	Same as IIB plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis	As above, more signs of generalized peritonitis, severe pain, abdominal distension	Same as IIB, plus definite ascites	Same as above, plus 200 ml/kg/day of fluids, inotropic agents, mechanical ventilation, paracentesis; if the patient does not improve within 24 to 48 hours, surgical intervention
IIIB ECN advanced. Seriously ill, intestinal perforation	Same as IIB plus hypotension, bradycardia, severe apnea, respiratory and metabolic acidosis combined, disseminated intravascular coagulation, neutropenia	As above, more signs of generalized peritonitis, severe pain, abdominal distension	Same as IIIA, plus pneumoperitoneum	Same as above, plus surgical intervention

Source: Hachem, Lyra, Scarpa, et al.[1]

is static, not allowing visualization or identification of the blood flow situation, where there is potentially an area subject to necrosis and perforation. The presence of air in the submucosa of the intestine, resulting from the fermentation produced by bacteria in addition to the intestinal lumen, is pneumatosis and can be visualized on X-rays. Distension of intestinal loops is the first sign to draw attention on imaging, and reflects the abdominal distension already seen clinically.[9] The radiographic study does not require a high-cost device, such as ultrasound, or a specialized professional to perform the exam, because not every neonatologist is prepared to perform ultrasound. On the contrary, the radiographic study is performed by a technician who waits to be reported later, but can be interpreted by the attending physician himself.[3]

It should always be borne in mind to provide the least radiation to the patient. Ultrasonography, in turn, uses high-frequency sound waves to give rise to an anatomical image. It is widely used to evaluate the central nervous system, presence of periventricular leukomalacea, intraventricular hemorrhage, i.e., hypoxic ischemic lesion, compatible with a history of fetal distress at birth.[3] Images may reveal a metabolically less active borderline zone, reflected by a deep gray image. Areas of tissue necrosis may appear in the form of cavitation, cysts, or decreased white matter. Intracranial hemorrhage may also be visualized, or areas of hydrocephalus may appear in the course. Neonatal heart diseases, which include structural abnormalities with consequent impairment of cardiac function and organ oxygenation, can be detected through echocardiography. Congenital heart tumors that cause obstruction of blood flow, congenital malformations, and pulmonary hypertension due to hypoxia or bronchial aspiration at birth may also be diagnosed.[3]

Treatment

Medical treatment should be initiated as soon as NEC is suspected and consists of initially transferring the newborn from rooming-in or intermediate inpatient unit to the neonatal ICU, placement in an incubator to avoid cross-infection, and close monitoring of vital data. Contact isolation and bowel rest measures should be installed by suspending feeding, prescribing fasting, placing a large gastric tube leaving it open to control gastric stasis, and prescribing parenteral nutrition to avoid severe weight loss. It is important to institute supportive measures, maintain fluid and electrolyte balance, cardiocirculatory support due to the risk of septic shock, respiratory support, and analgesia due to the discomfort and pain that may be present. All procedures must follow pre-existing protocols in the service according to the recommendations for infection control and based on the management practices of the little patient.[5,7]

Complementary tests should be requested to assist in the diagnosis and verification of elements that contribute to the decision of the treatment to be instituted. It is recommended to collect laboratory tests and cultures for the prescription of antibiotic therapy if necessary, monitoring the evolution and decision to change medication.[1,3,5]

Blood component replacement should be carefully evaluated, since authors suggest a relationship between blood transfusion and the pathogenesis of NEC, probably because it needs to be due to anemia that causes tissue hypoxia.[7]

Radiographic study for the acute abdomen (anteroposterior, lateral and supine views with horizontal rays) should be requested every 6/8 h, or abdominal ultrasound, and discussion of the neonatology team with the pediatric surgery about the imaging findings.[13]

The construction of medical records according to the evolutionary sequence is important for monitoring and decision-making, and should be carried out based on the results of complementary tests, laboratory tests, imaging, and the appearance or disappearance of new signs and symptoms. Recording the stage of the disease according to the modified Bell classification directs the clinical management, beginning of fasting or resumption of diet, initiation of antibiotic therapy, and the choice of drugs to be used or their suspension. Indicate the use of vasoactive drugs and surgical options, keeping in mind the prevention of sequelae and complications, such as short bowel. Precise surgical intervention is indicated

when pneumoperitoneum or paracentesis occurs with the presence of feces or bile; Relative indication is the presence of wall cellulitis, persistent fixed loop, fixed abdominal mass, diffuse pneumatosis (4 quadrants), and air in the portal system.

CONCLUSION

NEC affects premature babies, and the occurrence is greater the greater the prematurity. Low birth weight is also a predisposing factor, and the lower the weight, the greater the number of cases. Apgar below 7 on the 5th. minute of life and hypoxia during resuscitation can be inducers of his presence. Initial complementary diagnosis should be made by plain abdominal x-ray and ultrasound. In addition, transfontanelle ultrasound should be used when hypoxic brain injury is suspected, and echocardiogram to verify cardiac malformations that lead to intestinal hypoperfusion.

Authors' contributions

Wilma Lilia de Castro e Souza Silva: Conceptualization, Methodology
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BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e00006

Marfan and Ehlers-Danlos Syndrome: two collagenopathies with similarities and differences

Síndrome de Marfan e Ehlers-Danlos: duas colagenopatias com similaridades e diferenças

Julia Czelusniak[1], Fernanda Ritt de Souza[1], Yasmin de Sá Ortiz[1], Liya Regina Mikami[1], Heloisa Stadler Ribas[1]

ABSTRACT

Introduction: Marfan and Ehler-Danlos syndromes are diseases identified as collagenopathies, that is, they consist of defects in the production of collagen or in its modifying enzymes. Both syndromes present singularities.

Objective: To compare and differentiate Marfan and Ehler-Danlos syndromes regarding their pathophysiology and clinical manifestations.

Method: Literature review using 27 articles published in the last 15 years, in Portuguese and English. The inclusion criteria were to be the subject of collagenopathies, especially Marfan and Ehler-Danlos syndromes.

Result: 27 articles were used.

Conclusion: Among the collagenopathies, they are the most similar in relation to symptoms; however, they differ in treatment, which is specific to each one of them.

KEYWORDS: Marfan syndrome. Ehlers-Danlos syndrome. Collagen diseases. Treatment.

RESUMO

Introdução: Síndromes de Marfan e de Ehler-Danlos são doenças identificadas como colagenopatias, ou seja, são constituídas de defeitos na produção do colágeno ou em suas enzimas modificadoras. As duas síndromes apresentam singularidades.

Objetivo: Comparar e diferenciar as síndromes de Marfan e Ehler-Danlos quanto à sua fisiopatologia e manifestações clínicas.

Método: Revisão de literatura empregando 27 artigos publicados nos últimos 15 anos, nos idiomas português e inglês. Os critérios de inclusão foram ser o tema em colagenopatias, especialmente as síndromes de Marfan e de Ehler-Danlos.

Resultado: Foram utilizados 27 artigos.

Conclusão: Dentre as colagenopatias elas são as mais semelhantes em relação aos sintomas; porém, diferem-se no tratamento, que é específico a cada uma delas.

PALAVRAS-CHAVE: Síndrome de Marfan. Síndrome de Ehlers-Danlos. Doenças do colágeno. Tratamento.

Central message

Marfan and Ehler-Danlos syndromes are diseases identified as collagenopathies, that is, they are made up of defects in the production of collagen or its modifying enzymes. The two syndromes have singularities. The treatment is specific to each type and generally seeks to alleviate and treat complications caused by the absence or reduction of collagen in the body.

Perspective

These syndromes have more similarities than differences in relation to the affected tissue and symptoms. However, their differentiation is fundamental since the drug treatment is different and specific to each of them.

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Conflict of interest: None | Funding: None | Received: 17/11/2024 | Accepted: 22/01/2025| Publication date: 11/02/2025 | Correspondence: liyamikami@gmail.com | Associate Editor: Ronaldo Mafia Cuenca

How to cite:
Czelusniak J, de Souza FR, Ortiz YS, Mikami LR, Ribas HS. Síndrome de Marfan e Ehlers-Danlos: duas colagenopatias com similaridades e diferenças. BioSCIENCE. 2025;83:e00006

INTRODUCTION

Collagenopathies are genetic diseases that affect the production of various types of collagen in affected individuals. This can occur due to pathogenic variants in the FBN1 gene in Marfan syndrome, and mutations in 47 genes in Ehler-Danlos, which are responsible for the production of collagen or enzymes that modify this protein. Usually, these disorders are usually multisystemic, heterogeneous, and variable, causing damage to various organs, especially those with collagen-rich tissues; therefore, its symptoms are considerably varied.[1-3]

The treatment is specific to each type and generally seeks to alleviate and treat complications caused by the absence or reduction of collagen in the body.[4] Diagnosis is made by evaluation of symptoms and laboratory tests. In Marfan, echocardiograms/MRI, slit-lamp examinations, and genetic tests are performed. Similar methods are used for Ehlers-Danlos syndrome; however, DNA sequencing or sequencing of one/any of the related genes may be considered to confirm the specific type of disease.[5,6] It is noteworthy that because it is a very broad field of study and because collagenosis includes many diseases, there are no general standards for treatment and diagnosis for all of them, as both vary according to the patient's condition.

In the field of collagenopathies, Marfan and Ehlers-Danlos syndromes stand out for their similarities in symptoms and differences in treatment and in the form of collagen involvement.

Marfan's is caused by mutations in the FBN1 gene that encodes fibrillin-1, a glycoprotein present in the extracellular matrix in the form of microfibrils responsible for the elasticity of connective tissue.[7] One of the major problems arising from this condition is impending aortic aneurysm due to its abnormal dilation. In addition, manifestations in the muscular and skeletal systems are also common, including tall stature due to exaggerated bone growth, deformities related to sternum displacement, scoliosis, flat feet, dural ectasia, and joint laxity.[7] The eyes can also be affected by ectopia lentis and retinal detachment. The phenotypes of the syndrome may manifest in varying degrees and adequate follow-up may provide longer life expectancy.[8]

Ehler-Danlos syndrome, on the other hand, also affects 1 in every 5,000 live births and is caused by failure in the synthesis of some types of collagen (I, III or V). It is classified into 13 types, according to its effects, which vary greatly, reaching from the skin, more elastic than normal and with a greater propensity to bruises, has joints that are more flexible and more sensitive to injuries than normal and thinner blood vessels susceptible to rupture.[9]

Treatment aims to control symptoms and prevent simpler manifestations from evolving into more complex and harmful complications. Medical conduct varies according to the symptom, its intensity, specific clinical picture and involves treatment with beta-blockers, as in Marfan syndrome, pain control medication, physiotherapy to help preserve and prevent injuries, especially in the joints, and even surgical procedures, especially in cases where it is necessary to correct orthopedic problems.[9]

Both Marfan and Ehler-Danlos syndrome are rare genetic entities with the same incidence in live births, but although both are collagenopathies, they have collagen impairment differently.

Symptoms in Ehler-Danlos syndrome include joint hypermobility, abnormal scarring, wound healing, fragile vasculature, and hyperextensible smooth skin. The skin may be stretched several centimeters, but it returns to normal when released. In Marfan syndrome, patients are taller than average for their age, the arm span exceeds height and, in addition, they have arachnodactyly and deformity of the sternum (called "*pectus carinatum*" or "*pectus excavatum*").[5]

Therefore, both Marfan and Ehler-Danlos syndrome have their own singularities that differentiate them from other collagenopathies, and similarities between them, which create a complex connection between the 2 diseases.

Thus, this study aimed to analyze the correlation between the 2 syndromes, focusing on their similarities and differences, in order to assist physicians and other health professionals in their differentiation for accurate diagnosis and, mainly, appropriate pharmacological treatment.

METHOD

This is a narrative review of the literature in which review articles and case reports from 2009 to 2024 were used, in Portuguese and English. In the search, the Scielo, PubMed, Google Scholar and Capes Periódicos databases were consulted, through the application of the following descriptors: Marfan syndrome, Ehlers-Danlos, collagen diseases and treatment. The inclusion criteria were articles and books related to collagenopathies, focusing on the general description or treatment of Marfan and Ehlers-Danlos syndromes, resulting in 25 articles that were included in this study.

DISCUSSION

Marfan syndrome

First described in 1896 by French pediatrician Antoine Bernard-Jean Marfan, it affects about 1 in every 5,000 live births, with no predominance of sex or ethnicity. It is a rare autosomal dominant disease with incomplete penetrance that affects the connective tissue, specifically its matrix, due to alterations in collagen synthesis.[4,7,8] The condition is caused by mutations in the FBN1 gene, on chromosome 15q21.1, which alters the amount and structure of collagen.[4,8,10] This gene is responsible for encoding the fibrillin-1 protein, a component of the structure of the microfibrils (10-12 nm in size) of the extracellular matrix, which are essential for the elasticity and tensile strength of the connective tissue.[5,11]

Thus, the main symptoms involve the cardiovascular, musculoskeletal, ocular, pulmonary and central

nervous system systems.[5] Another striking characteristic is that those affected feel a lot of muscle pain, which significantly decreases their quality of life.[12] Therefore, it is important to diagnose early and accurately so that the appropriate medication is prescribed and brings more comfort to the patient. Also, Marfan syndrome is underdiagnosed and therefore the importance of analyzing and knowing its characteristics, in addition to the similarities and differences with other collagenopathies, such as Ehler-Danlos.[4]

Some of the most common manifestations of the syndrome are mitral valve prolapse, which can cause mitral regurgitation, and is often the earliest and most severe symptom of Marfan syndrome, since it can bring more severe insufficiency and lead to death in childhood, and dilation of the descending aorta, usually later, and that it can cause, in addition to mitral regurgitation, aortic regurgitation and rupture. Because it has a higher concentration of elastic fibers, the root of the aorta is more prone to dilation, a typical characteristic of the condition.[13]

As for the musculoskeletal system, the most characteristic and common manifestation is arachnodactyly, which is configured by the presence of long and slender fingers, thoracic deformities, high joint flexibility, scoliosis and hard palate, which causes arching of the teeth.[13] Abnormal TGF-β signaling resulting from changes in the FBN1 gene is responsible for abnormal bone development and osteoporosis development, as it results in irregularities in osteogenesis and osteoclast activity. Exaggerated bone growth causes spinal problems (especially scoliosis) to appear more frequently in patients with Marfan syndrome. However, surgical procedures for its correction are significantly riskier in individuals with the disease.[7]

The diagnosis of Marfan syndrome requires a broad analysis of several factors of the patient, analyzing family history, tests such as complete anthropometry, accurate ophthalmologic examination with a slit lamp, chest X-ray (for visualization of the spine and sternum) and echocardiography.[13] The main form of diagnosis is Ghent nosology, involving the analysis of several factors, including affected family members and manifestations of the disease. This analysis consists of a test with scores up to 20, and it is necessary to evaluate the presence of certain symptoms and family history in determining the reference value, z-score, for the diagnosis (Table). These criteria were improved in 2010 so that the diagnosis would be more accurate.[4,8]

Early diagnosis is essential for a better prognosis, since its manifestations are progressive and irreversible. When the disease is detected early, many complications can be avoided, increasing the life expectancy of the carrier.[4,8] This diagnosis tends to be more difficult in childhood, as certain symptoms only manifest in adulthood. Therefore, children with suspected Marfan syndrome should be followed up regularly to monitor symptoms.[4,8]

Other factors that may make diagnosis difficult are highly variable inter- and intrafamilial expressiveness; certain clinical manifestations being age-dependent; large number of *de novo* mutations; and clinical overlap with several other connective tissue diseases.[8]

TABLE— Ghent nosology simplified, with the main clinical characteristics and respective scores

No family history	With a family history
Aortic root ≥, +2 z-score, and ectopy of the crystalline	Lens ectopy
Aortic root ≥, +2 z-score, and aortic mutation Fibrillin-1 (BNF-1)	Systematic score ≥ 7
Aortic root ≥, +2 z-score and score systemic ≥ 7.	Aortic root ≥, +3 z-score if < 20 years old. Or ≥ aortic root, +2 z-score if > 20 years.
Lens ectopia and mutation of the Fibrillin-1	

Characteristic	Quantity points
Fist and thumb sign	3
Pectus carinatum	2
Protrusion of the acetabulum	2
Pneumothorax	2
Dilatation of the dura mater	2
Retrope deformity	1
Wrist or thumb sign	1
Low elbow joint extension movement	1
Flat feet	1
Stretch marks on the skin	1
Scoliosis or problems related to the position of the spine vertebral	1
Increased length of the upper limbs and height	1
Myopia	1
Oblique palpebral clefts	1
Mitral valve prolapse	1

Regarding treatment, those affected are advised not to smoke, pay attention to their blood pressure and avoid high-intensity sports.[8] Musculoskeletal symptoms are usually treated with occupational therapies or physical therapy, without the need for medication, and for aortic complications, beta-blockers are used, which are prescribed to all those affected by Marfan syndrome, including children. Such drugs reduce the heart rate and reduce hemodynamic stress on the aortic wall, preventing its dilation and dissection, and reducing the risk of the appearance of other cardiovascular complications, as well as the need for surgical intervention in the myocardium.[8] The most significant risk of Marfan syndrome is associated with aortic dilation with the eventual development of an aneurysm.[7] Consequently, its treatment is more urgent and, in most cases, indispensable. Losartan is an angiotensin II type I receptor antagonist that has been shown to prevent progressive dilation of the aortic wall. In addition to its antihypertensive action, the drug induces a reduction in plasma levels of TGF β. In addition, losartan does not interfere with the angiotensin II type II receptor, which is responsible for anti-inflammatory and antiproliferative effects, maintaining the homeostasis of the aortic wall and helping to prevent aneurysms.[8]

When aortic dilation becomes a risk factor, the Bentall procedure is recommended, which consists of replacing the aortic valve with a mechanical valve, also called a composite valved graft, and which subsequently requires the continuous use of anticoagulants such as warfarin.[7,14]

In addition, the nature of Marfan syndrome makes conditions such as myopia and astigmatism common among affected individuals. Its treatment is simple,

and it is possible to resort to correction lenses.[7] During childhood, it is recommended to visit medical geneticists and cardiologists. In addition, periodic visits to pediatric cardiologists and annual examination of the aorta should occur, in cases where the size of the aortic root exceeds 4 cm or with high growth of 0.5 cm per year, it is recommended that these examinations be performed every six months.[7] In adulthood, monitoring should remain constant to avoid complications and, if they arise, treat them as soon as possible. Pressure should be controlled and preferably kept below 130/80 mmHg in order to avoid hypertensive conditions and certain medications such as hydralazine, calcium channel blockers and fluoroquinolones, which are associated with increased aortic dissection and increase the risk of aneurysm. Also, sports such as diving and those related to extreme heights are not recommended due to the risk of spontaneous pneumothorax.[7] The prognosis of carriers is relatively good, if diagnosis and treatment are early. With the use of beta-blockers, the life expectancy of patients can reach more than 72 years.[8] In addition, although it is a possible way to relieve problems related to the spine (such as scoliosis, common in Marfan), surgical repair of the spine poses great risks to those with Marfan syndrome, which can interfere with their quality of life.[7] In general, those affected will have their way of life affected by the multisystem complications resulting from the disease. Despite this, it is possible for the individual to have a long survival, if appropriate treatment is given.

Ehler-Danlos syndrome

This syndrome is a set of diseases with predominantly autosomal dominant inheritance, with great genetic heterogeneity[15] caused by mutations in about 47 genes that encode proteins that act in the formation of connective tissue. They are: ADAMTS2, AEBP1, ALDH18A1, ATP6V0A2, ATP6V1A, ATP7A, B3GALT6, B4GALT7, BGN, C1R, C1S, CBS, CHST14, COL12A1, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, COL6A1, COL6A2, COL6A3, DSE, EFEMP2, ELN, FBLN5, FBN1, FBN2, FKBP14, GORAB, LOX, LTBP4, PLOD1, PRDM5, PYCR1, RIN2, ROBO3, SKI, SLC39A13, SMAD2, SMAD3, TGFB2, TGFB3, TGFBR1, TGFBR2, TNXB, ZNF469.[3] Its incidence ranges from 1 in 2,500 to 1 in 5,000 individuals.[16]

It is characterized by hypermobility of the joints, hyperelastic skin, slow healing, fragility of tissues, and frequent dislocations or subluxations after minor traumas.[12,17] Due to these changes, those affected feel a lot of muscle pain and the arterial fragility of the organs can cause premature death.[12,18] There are also cardiac, neurological and psychological complications.[12]

In 2017, the international classification of diseases that make up Ehlers-Danlos syndrome (EDS) was created, which were divided into 13 subtypes, some of which stand out for having characteristics, similar to Marfan syndrome. Such subtypes are: classic EDS, cardiac-valvular EDS, vascular EDS, arthrolasia EDS, kyphoscoliotic EDS, fragile corneal syndrome, and musculocontractural EDS. In these subtypes, some characteristics and symptoms present in patients are very similar and should be carefully analyzed, such as complications of joint hypermobility, severe progressive heart valve problems (aortic valve, mitral valve), arterial rupture, pneumothorax, kyphoscoliosis, rupture/aneurysm of a medium-caliber artery, chest deformity, refractive errors (myopia, hyperopia), retinal detachment, scoliosis, and arachnodactyly.[5,19]

Regarding its treatment, multidisciplinary conduct is indicated, including physical and occupational therapy and preventive care for the complications generated by the disease.[12] Regarding arterial fragility, celiprolol is used. The studies by Franck et al.[18] demonstrated that patients treated with celiprolol had a higher survival rate, which depended on the dose received of the drug, compared to those who did not use this medication ($p = 0.0004$).

Marfan syndrome vs Ehler-Danlos syndrome

The syndromes chosen for this review were Marfan and Ehler-Danlos syndromes due to their symptomatic similarities, but distinct in treatments in certain aspects. Both affect the body's connective tissues, generating several complications in common systems, such as cardiac and ocular systems. Despite this, the treatment for these collagenoses, although it coincides with certain complications, is different, since the genes affected by each one is particular, as well as the way in which these genetic alterations affect each part of the organism.

When compared to other collagenopathies, there is a variety in manifestations within the group, with several diseases with the most varied symptoms, such as rheumatoid arthritis (joint pain, small peripheral joints, edema, general stiffness and weakness, subcutaneous rheumatoid nodules, bronchiolitis and interstitial lung disease)[20,21], progressive systemic sclerosis (inflammation, vasculopathy, and cutaneous and visceral fibrosis, with collagen deposits in the dermis and thickening of collagen fibers)[21], and dermatopolymyositis (interstitial inflammatory infiltrate, non-specific interstitial pneumonia, organizing pneumonia, deep alveolar damage, and muscle necrosis).[22,23]

One of the similarities between Marfan and Ehler-Danlos is in their classification, since both are collagenopathies, as they affect collagen synthesis.[7,9] Treatment involves the management of beta-blockers to avoid complications related to dilation and possible rupture of the arteries.[7,24] In EDS, the commonly prescribed medication is celiprolol - reducing heart rate and blood pressure, and consequently, also reducing the mechanical stress applied to the arterial walls. In Marfan syndrome the most commonly used drug is losartan, which decreases plasma levels of TGF-β. However, in experimental studies, it did not present significant effects in rats induced for Ehler-Danlos syndrome, configuring one of the differences between the 2 syndromes.[25]

Ocular involvement can also occur in both diseases. However, this symptom is different for each of them. In Marfan syndrome, there is an alteration in the lens (subluxated or displaced upwards) and in EDS, there is involvement and fragility of the sclera, resulting in

perforation of the eyeball in severe cases.[5]

Symptoms affecting the musculoskeletal system are also similar in the 2 syndromes, especially spinal deformities (scoliosis, congenital or early-onset kyphoscoliosis, which can be progressive or non-progressive), chest deformity, arachnodactyly, complications of joint hypermobility (e.g., sprains, dislocation/subluxation, pain, and flexible flat foot).[7,19] Lifestyle is also shaped in a similar way between individuals with both diseases. Cardiac and musculoskeletal frailty implies that those affected avoid playing very intense sports.[8] In addition, the treatment of Marfan syndrome and Ehler-Danlos syndrome involves a multidisciplinary scope, with an approach that mainly aims to help reverse and avoid possible complications in the systems compromised by the diseases, with the cardiac system being the system that requires the most attention because it has more severe complications.

CONCLUSION

Marfan and Ehler-Danlos syndromes are collagenopathies caused by mutations in genes involved in collagen synthesis or in the enzymes responsible for its structure. These syndromes have more similarities than differences in relation to the affected tissue and symptoms. However, their differentiation is fundamental since the drug treatment is different and specific to each of them.

Authors' contributions

Julia Czelusniak: Conceptualization, Writing (review and editing)
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Heloisa Stadler Ribas: Writing (review and editing)

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BioSCIENCE Original Article
DOI: https://doi.org/10.55684/2025.83.e00007

Conditions requiring parenteral nutrition in high-risk newborns

Condições que demandam nutrição parenteral em recém-nascidos de risco

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ABSTRACT

Introduction: Some at-risk newborns (NBs) face complications that make enteral feeding unfeasible, especially those admitted to the neonatal intensive care unit (NICU). In these cases, parenteral nutrition (PN) is essential to provide adequate nutritional support for development until they can progress to exclusive oral feeding.

Objective: To evaluate the causes and conditions that require PN in at-risk newborns, describe their clinical characteristics, and analyze the complications resulting from this type of nutrition.

Method: A cross-sectional and retrospective study, carried out by collecting data from medical records of all newborns who used PN in the neonatal ICU during the year 2022.

Result: Of the 686 hospitalized at-risk newborns, 20% used PN for a median time of 8 days. The causes and indications for its use were classified into 4 categories: 1) prematurity; 2) malformations of the gastrointestinal tract; 3) major operations; 4) adynamia. Regarding complications, there were 18 cases of cholestasis and 18 cases of catheter infection. Eighteen newborns on PN died. The cost of the PN solution in the neonatal ICU was approximately 7 times higher than that of enteral feeding.

Conclusion: The conditions that require PN in high-risk newborns can be grouped into: prematurity, malformations of the gastrointestinal tract, major surgeries, and conditions of gastrointestinal adynamia. The 2 main complications observed were cholestasis and catheter infection.

KEYWORDS: Parenteral nutrition. Neonatal intensive care units. Prematurity.

Central message

Parenteral nutrition is essential to meet the nutritional needs of at-risk newborns in neonatal ICUs, particularly those with extreme prematurity or severe clinical conditions. Thus, parenteral nutrition provides the necessary nutrients when enteral feeding is not viable. Therefore, identifying the conditions that lead to this need is essential to improve neonatal care and reduce possible complications.

Perspective

It is essential that health professionals and hospital managers recognize the importance of adequate parenteral nutrition and its correct implementation. In addition, investing in training and protocols for its use can ensure that vulnerable newborns receive the necessary nutrition, promoting healthy development.

RESUMO

Introdução: Parte dos recém-nascidos (RN) de risco enfrentam complicações que inviabilizam a alimentação com dieta enteral, especialmente os internados em unidade de terapia intensiva (UTI) neonatal. Nesses casos, a nutrição parenteral (NP) é essencial para fornecer o aporte nutricional adequado ao desenvolvimento até que consigam evoluir para alimentação oral exclusiva.

Objetivo: Avaliar as causas e condições que demandam NP em RN de risco, descrever suas características clínicas e analisar as complicações decorrentes desse tipo de nutrição.

Método: Estudo com delineamento transversal e retrospectivo, realizado através da coleta de dados de prontuários de todos os RN que utilizaram NP em UTI neonatal durante o ano de 2022.

Resultado: Dos 686 RN de risco hospitalizados, 20% fizeram uso de NP por tempo mediano de 8 dias. As causas e indicações para o seu uso foram classificadas em 4 categorias: 1) prematuridade; 2) malformações do trato gastrointestinal; 3) grandes operações; 4) adinamia. Quanto às complicações, ocorreram 18 casos de colestase e 18 de infecção do cateter. Dezoito RN em NP evoluíram para óbito. O custo da solução de NP na UTI neonatal foi cerca de 7 vezes maior do que seria aquele da alimentação enteral.

Conclusão: As condições que demandam NP em RN de risco podem ser agrupadas em: prematuridade, malformações do trato gastrointestinal, grandes operações, condições de adinamia gastrointestinal. As 2 principais complicações observadas foram colestase e infecção do cateter.

PALAVRAS-CHAVE: Nutrição parenteral. Unidades de terapia intensiva neonatal. Prematuridade.

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Conflict of interest: None | Funding: None | Received: 17/11/2024 | Accepted: 22/01/2025 | Publication date: 24/02/2025 | Correspondence: aristides.schier@terra.com.br | Associate Editor: Fernando Issamu Tabushi

How to cite:
Arcie GM, Custódio P, da Cruz AS, Rocha JAS, Brites TAM. Condições que demandam nutrição parenteral em recém-nascidos de risco. BioSCIENCE. 2025;83:e00007

INTRODUCTION

Of all newborns (NB), a high proportion has complications that justify hospitalization in the neonatal intensive care unit (ICU). They are called newborns at risk, with multiple morbidities. The vital processes demanded by the organism of the newborn at risk require an adequate amount of nutrients and energy for the development of their systems.[1,2] However, for multiple reasons, it is not possible to administer nutrients orally or enterally in a significant part of these children.[3,4] When such situations occur, the method of ensuring that the newborn receives adequate nutritional intake is parenteral nutrition (PN), alone or concomitantly with enteral nutrition.[5] It must contain carbohydrates, amino acids, lipids, vitamins and minerals, that is, it must be nutritionally complete. The early use of PN helps the NB to maintain adequate nutritional status, until the enteral route becomes viable for 100% of the nutritional needs. Inappropriate use, or non-use, of PN can promote short- or long-term growth or development deficits in childhood.[6-8]

It is likely that there is a long list of indications for the administration of PN in at-risk NB, and of the various organic conditions that make exclusive enteral nutrition unfeasible for some time. It seems important that neonatologists and intensivists who care for NB at risk have the opportunity to evaluate an epidemiological overview of the conditions that demand PN, whether malformations of the gastrointestinal tract, major surgeries, prematurity and other situations that promote enteral food intolerance.

The present study aimed to evaluate, in a reference hospital for high-risk pregnant women, the neonatal conditions that require PN in newborns at risk in neonatal ICU, to describe their clinical characteristics, the complications resulting from the use of PN and to estimate the costs of this method of neonatal nutrition.

METHOD

This was a cross-sectional and retrospective study, with analysis of the electronic medical records of NBs from the Obstetric and Neonatal Center of the Mackenzie Evangelical University Hospital (HUEM) in Curitiba, PR, Brazil, who required PN during some time of their hospitalization in the neonatal ICU between January 1 and December 31, 2022. The research project obtained a favorable opinion from the Human Research Ethics Committee of the Mackenzie Evangelical College of Paraná.

All at-risk NB of both sexes who started receiving PN solution infusion were included. The electronic medical record of each person who had received PN in 2022 was thoroughly reviewed in order to tabulate data from several categorical and continuous variables related to the patient's general characteristics, establish the probable reasons that led to the indication of PN, and the possible complications of its use.

Statistical analysis

The data compiled were tabulated in an Excel spreadsheet. Categorical variables were presented as numbers, percentages, and 95% confidence intervals (95%CI). Continuous variables were presented as mean and standard deviation, or median and interquartile range (IQR).

RESULT

In 2022, 686 newborns required admission to the neonatal ICU, of which 140 (20.4% - 95%CI 17.[4] to 23.4%) used PN for some time. The median time of PN use was 8 days, ranging from 1 to 93 days (IQR 5 - 16 days). Table 1 lists the quantitative variables of the 140 NB at risk who received PN. Table 2 lists the categorical variables analyzed.

TABLE 1 – Quantitative variables analyzed in the 140 newborns at risk submitted to PN

Quantitative variables	Mean (SD)	Median	IIQ I - III
Gestational age (weeks)	33,1 (4)	33	31 - 37
Birth weight (g)***	1.892 (837)	1.775	1298 - 2411
Height at birth (cm)	40,6 (6,1)	41	36,5 - 44
APGAR 1st min	5,8 (2,5)	7	4 - 8
APGAR 5th min	7,8 (1,9)	8	8 - 9
NP Usage Time (days)	13,7 (15)	8	5 - 16
Length of stay (days)	50 (41,1)	37	22 - 65

*IQR I – lower interquartile range, which is equivalent to the 25th percentile of the sample; **IQR III – upper interquartile range, which is equivalent to the 75th percentile of the sample; The birth weight range was from 505g to 4235g.

TABLE 2 – Categorical variables analyzed in the 140 newborns at risk submitted to PN

Categorical variables	n (%)	95% CI
Cesarean delivery	103 (73,6%)	66.3 to 80.9%
Male	74 (52,8%)	44.6 to 61.1%
Respiratory failure	134 (95,7%)	92.4 to 99.1%
Mechanical ventilation	98 (70%)	62.4 to 77.6%
CPAP*	112 (80%)	73.4 to 86.6%
Antibiotics	139 (99,3%)	-
Blood transfusion	94 (67,1%)	59.4 to 74.9%
Sepsis	34 (24,2%)	17.2 to 31.4%
Other infections**	85 (60,7%)	52.6 to 68.8%
Central catheter	120 (85,7%)	79.9 to 91.5%
Death	18 (12,9%)	7.3 to 18.4%

* CPAP: Continuous positive airway pressure; ** Other infections: other infectious clinical conditions, other than sepsis, early or late.

Of the 140 patients who received PN, 103 (73.6%) were born preterm (gestational age <37 weeks). Considering that the PN indication protocol differs according to the range of prematurity, Table 3 presents the prematurity classification of the patients included in the study.

TABLE 3 – Classification of prematurity in 103 of the 140 NB submitted to PN

Gestational age	n (%)	95%CI
<32 weeks*	48 (34,3%)	26.4 to 42.1%
32-34 weeks**	41 (29,3%)	21.7 to 36.8%
35 and 36 weeks***	14 (10%)	5.0 to 15.0%

* PN was offered to newborns with gestational age <32 weeks before the first 24 h of life, until enteral feeding of 100 mL/kg/day was reached; ** NP was administered to individuals with a gestational age of 32 to 34 weeks on the first day of life, trying to insert enteral diet concomitantly, until good acceptance of enteral diet was established (around 80 ml/kg/day); PN was administered to newborns with gestational age >34 weeks until the 5th day of life when there was an aggravation that promoted food intolerance.

Table 4 presents the causes and conditions associated with the use of PN in the 140 patients. The major indications of PN in newborns at risk were grouped into 4 main conditions: 1) high prematurity; 2) malformations of the gastrointestinal tract that would prevent enteral nutrition; 3) large operations that make enteral nutrition unfeasible for some time; 4) conditions that induce adynamic ileus or enteritis, due to potential wall ischemia or hypoxia, dysbiosis, bacterial overgrowth, or intestinal infection (a condition often called food intolerance).

TABLE 4 — Causes and conditions associated with the use of PN in the 140 patients (includes patients who had 2 or more causes and conditions)

Causes	n=140	%
Birth weight <1500g*	49	35%
Prematurity <32 weeks*	48	34,3%
Severe respiratory failure**	91	65%
Sepsis**	34	24,2%
Food intolerance***	30	21,4%
Perinatal anoxia**	19	13,5%
Major surgery*****	18	12,8%
Severe congenital heart disease**	15	10,7%
GIT malformation****	13	9,3%
Necrotizing enterocolitis**	11	7,8%
GIT infection**	8	5,7%
Meconium ileus	1	0,7%
Short bowel syndrome	1	0,7%

* Prematurity <32 weeks and birth weight <1500 g are primary conditions that require the protocol use of PN, indicated until the newborn is able to reach enteral feeding of 100 ml/kg/day; **clinical conditions that can cause ischemia or oxygen deficiency in the intestinal wall, inducing adynamic ileus, making enteral feeding impossible, and promoting bacterial overgrowth in the small intestine (necrotizing enterocolitis is the most severe form of this pathophysiological condition); denomination when it is unfeasible to continue feeding the newborn enterally due to gastric stasis, vomiting, abdominal distension or difficulty in evacuation (this situation is often caused by the same conditions described above, in **); malformations of the gastrointestinal tract that prevented enteral nutrition, most of them requiring major operations: congenital megacolon (n=4); gastroschisis (n=4); esophageal atresia type C (n=3); laryngomalacia (n=1); diaphragmatic hernia (n=1); Major operation: situations in which, in the postoperative period, enteral feeding becomes unfeasible for some time, operation to correct digestive malformation (n=10); cardiovascular surgery (n=4); gastrointestinal surgery due to complications of necrotizing enterocolitis (n=3); extensive thoracic surgery due to pulmonary malformation and pneumonectomy (n=1).

Complications associated with PN were cholestasis in 18 cases (12.9% - 95%CI 7.[3] to 18.4%) and catheter infection in 18 cases (12.9% - 95%CI 7.3 to 18.4%), all by the Gram-positive Staphylococcus epidermidis bacteria. Death occurred in 18 cases (12.9%), of which 16 had infections (9 of them with sepsis), 7 with birth weight less than 1,000 g, 1 with gastrointestinal malformation and several surgeries, 1 with a major corrective procedure for congenital heart disease, and 3 with malformations (renal, chromosomal disease, genetic syndrome).

Considering the value of R$ 0.10 per calorie and the administration of 100 kcal/kg/day, for the 140 patients with a mean weight of 1,892 g and a mean PN time of 13.7 days, it can be estimated that the costs of parenteral nutrition (without considering the catheter and other related equipment) were R$ 36,288.00. In comparison, if these patients had received enteral nutrition in that period, the expense would have been R$ 5,443.00.

DISCUSSION

In this study on the use of PN in 140 NB at risk in a large neonatal ICU, it was possible to group the causes and conditions that demanded PN into 4 major categories: 1) newborns with prematurity of 34 weeks or less (n=89); 2) GIT malformations that prevented enteral nutrition for some time (n=13); 3) major operations that prevented enteral nutrition for some time (n=18); 4) conditions that induced gastrointestinal adynamia and required the establishment of a period of enteral fasting, due to ischemia or hypoxia of the intestinal wall, dysbiosis, or intestinal bacterial overgrowth, caused by extreme prematurity, respiratory failure, severe infection, congenital heart disease (the vast majority of the 140 patients in PN had this condition, but the extreme form was necrotizing enterocolitis, which occurred in 11 cases, 3 of which required intestinal operation). One patient suffered the classic and severe form of prolonged PN requirement known as intestinal failure, due to short bowel syndrome, secondary to intestinal malrotation and massive necrosis. The 4 major categories of conditions that demand NP in the RN at risk, classified above, are not watertight. Certainly, in most cases, the NP indication fit into 2 or more categories.

Prematurity is associated with very peculiar anatomical and physiological characteristics. The younger the gestational age, the more difficult the neurological, respiratory, circulatory, and dietary functions, and the greater the risks of bacteremia and infection. The nutritional goal in premature newborns is to achieve postnatal growth at a rate that is comparable to the growth and intrauterine weight gain of a normal fetus of the same gestational age, avoiding nutritional deficiencies, metabolic complications or toxicity due to the exaggerated nutritional supply.[9,10] In the present study, 74% of the patients were born prematurely. Studies carried out in Ceará and Pernambuco, Brazil, documented a high proportion of prematurity among at-risk NB receiving PN. [11,12] In the present study, a large proportion of the NB using PN were born with GIT malformations, or required major surgeries. One patient was born with meconium ileus, 3 required laparotomy for severe necrotizing enterocolitis, and 1 suffered massive intestinal necrosis due to intestinal malrotation. The considerable demand for GIT operations in the NICU is also documented in other publications.[11,12]

Situations of food intolerance, in which the neonatologist establishes a period of fasting and administration of PN, are very common in critically ill patients in the neonatal ICU. It is quite common for such situations, caused by ischemia or anoxia of the intestinal wall, bacterial overgrowth, intestinal dysbiosis, to course with gastrointestinal adynamia, gastric stasis, vomiting, abdominal distension or bleeding in the stool as an immune response to intestinal dysbiosis.[13] It has often happened that such cases are treated with a specific food formula for cow's milk protein allergy, even though this type of allergy is very rarely present in newborns at risk. The comorbidities of the high-risk NB described in the present study are the real responsible for the symptoms of food intolerance.[14,15]

Almost all of the NB studied were affected by respiratory failure for some time, of which 73% required mechanical ventilation and 83% CPAP. A fifth were affected by sepsis, and 61% by other infections. The vast majority (99%) received prophylactic antibiotics or dressings.

Complications of PN are classically divided into 3 groups: mechanical or technical, metabolic, and infectious. Mechanical complications may be related to PN infusion, which may cause extravasation in the pericardium, peritoneum, and may also be linked to the catheter, causing pneumothorax, hemothorax, vascular lesions, air embolism, local and systemic infections, and superficial phlebitis.[16,17] Metabolic complications may be related to the type of nutrient administered, and there may be deficiency or elevation of the plasma level of certain substances, in addition to hepatic involvement and cholestasis.[16,17] In the present study, the review of medical records did not allow the reliable detection of possible mechanical or technical complications. However, 18 cases of PN-associated cholestasis and 18 cases of catheter-associated infections were confirmed. The longer the time of administration of PN, the greater the occurrence of infectious complications. As for infections, what differs from the literature is the type of bacteria found, since the predominance of S. aureus is documented, while in this study S. epidermidis was highlighted.[16] It was not possible to attribute the 18 deaths as a direct complication of PN, as they were patients with several very severe primary clinical conditions.

Regarding the cost of PN, it should be taken into account that it is used in a small proportion of hospital patients and for a limited time, when compared to enteral nutrition. Even so, studies show that total hospital expenditure on PN is 2.[2] times higher than that of enteral nutrition. In fact, the cost of PN solution in the patients evaluated in the present study was estimated to be about 7 times higher than the amount that would be spent on enteral formula in the period in which each patient received PN.[18]

As a limitation of this research, the obtaining of data from the neonatal ICU discharge records is highlighted, which makes reasonable heterogeneity inevitable in the way of describing and documenting the various clinical signs, symptoms or procedures. Despite this, it was surprising how much the reports in the medical records of at-risk NBs end up being filled out in a rich way in detail, compared to the medical records of patients from other hospital sectors. A striking peculiarity was the fact that, unlike most hospitals with a maternity sector, the hospital in this study is a referral center for high-risk pregnant women, with an expectation of a higher probability of morbidities that justify admission to the neonatal ICU, and neonatal mortality. The task of determining a single cause for the use of PN in each patient becomes complex, as several NB seem to present multiple factors that require the administration of parenteral nutrition.

The small number of scientific studies published on PN in at-risk NB reinforces the importance of the research presented here, which sought to improve knowledge about the main indications for parenteral nutrition, its complications and its cost.

CONCLUSION

In 2022, the administration of PN was performed in 20% of the total number of newborns hospitalized in the neonatal ICU of a hospital that receives high-risk pregnant women. The conditions analyzed that required the use of PN were: 1) newborns with prematurity of 34 weeks or less (n=89); 2) malformations of the gastrointestinal tract that prevented exclusive enteral nutrition (n=13); 3) major operations that prevented exclusive enteral nutrition (n=18); 4) conditions, commonly called food intolerance, which induced gastrointestinal adynamia and forced the establishment of a period of enteral fasting, due to ischemia or hypoxia of the intestinal wall, dysbiosis, or intestinal bacterial overgrowth (they course with gastric stasis, abdominal distension, vomiting, streaks of blood in the feces, and in its extreme form necrotizing enterocolitis). The most common complications associated with PN were catheter infection and cholestatic syndrome.

Author´s contributions

Gabriella Mara Arcie: Conceptualization, Writing (original draft)
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João Arthur Sachser Rocha: Conceptualization, Writing (original draft)
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Thaís Ariela Machado Brites: Investigation, Writing (original draft)

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BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e00008

Como contornar o impacto das doenças genéticas na vida dos pacientes e seus familiares?

How to overcome the impact of genetic diseases on the lives of patients and their families?

Fernanda Ritt de Souza[1], Cornélio Schwambach[2], Liya Regina Mikami[1]

RESUMO

Introdução: As doenças genéticas raras trazem desafios quanto a seu diagnóstico e tratamento. Muitos de seus sintomas são similares aos de doenças comuns, o que tende a atrasar o diagnóstico correto. Desse modo, o descobrimento e tratamento adequado da doença costuma decorrer de processo longo, cansativo e oneroso, gerando impactos psicoemocionais a todos os envolvidos.

Objetivo: Revisar o impacto psicoemocional sofrido pelos afetados e seus familiares por doenças genéticas raras durante o processo saúde-doença.

Método: Trata-se de revisão narrativa empregando artigos em português e inglês obtidos por meio de plataformas virtuais de pesquisa através dos descritores: "doenças raras", "doenças genéticas", "estresse psicológico", "tratamento" e "diagnóstico".

Resultados: Utilizou-se 20 artigos, sendo eles lidos e resumidos. Foram utilizados artigos publicados entre 2000 a 2024.

Conclusão: Considerar os impactos emocionais, caracterizados pela tristeza, ansiedade e frustração, desencadeados pelos desafios rumo ao diagnóstico e tratamento de doenças genéticas raras é essencial ao atendimento íntegro e adequado ao paciente.

PALAVRAS-CHAVE: Doenças genéticas raras. Impacto psicoemocional. Diagnóstico. Tratamento.

ABSTRACT

Introduction: Rare genetic diseases pose challenges in terms of diagnosis and treatment. Many of their symptoms are similar to those of common diseases, which tends to delay correct diagnosis. Thus, the discovery and appropriate treatment of the disease usually involves a long, tiring and costly process, generating psycho-emotional impacts for all involved.

Objective: To review the psycho-emotional impact suffered by those affected and their families by rare genetic diseases during the health-disease process.

Method: This is a narrative review using articles in Portuguese and English obtained through virtual research platforms using the descriptors: "rare diseases", "genetic diseases", "psychological stress", "treatment" and "diagnosis".

Results: Twenty-one articles were used, which were read and summarized. Articles published between 2000 and 2024 were used.

Conclusion: Considering the emotional impacts, characterized by sadness, anxiety and frustration, triggered by the challenges towards the diagnosis and treatment of rare genetic diseases is essential for comprehensive and appropriate patient care.

KEYWORDS: Rare genetic diseases. Psycho-emotional impact. Diagnosis. Treatment.

Central message

The necessary care with the impact of genetic diseases on the lives of patients and their families does not consist only of the treatment of their rare condition, but also of psychological attention, since the "odyssey" in search of the diagnosis generates considerable mental and emotional exhaustion, both for them and for their families.

Perspective

It is evident the need not only for the treatment of rare genetic diseases so that their carriers can be inserted into society and overcome their social difficulties, but also for psychological monitoring of patients and their families so that they are able to face the difficulties and challenges arising from the condition and the non-acceptance of the individual by society.

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Conflict of interest: None | Funding: None | Received: 17/11/2024 | Accepted: 22/01/2025 | Publication date: 24/02/2025 | Correspondence: liyamikami@gmail.com | Associate Editor: Rafaela Fernandes Gonçalves

How to cite:
de Souza FR, Schwambach C, Mikami LR. Como contornar o impacto das doenças genéticas na vida dos pacientes e seus familiares? BioSCIENCE. 2025;83:e00008

INTRODUCTION

Genetic diseases are conditions inherited or caused by mutations again in certain genes throughout life. They are usually challenging in terms of their diagnosis and treatment due to their complexity and about 80% of them are considered rare diseases, characterized by affecting 1.3 people per 2000 individuals. These diseases are usually difficult to diagnose, as they manifest symptoms similar to those of common diseases and can be multisystemic, causing doubts in doctors about the diagnostic hypothesis and leading to mistaken treatments. In addition, many health professionals do not have sufficient mastery and knowledge about rare genetic conditions, aggravating the situation. In this way, several patients receive late diagnoses, after traveling a long and costly journey, full of excessive and unnecessary consultations and exams in search of treatment for their condition. There are cases in which the disease caused irreversible damage to the affected person due to the delay in treatment.[1-5]

In this sense, the necessary care does not consist only of the treatment of his rare condition, but also of psychological attention, since the "odyssey" in search of the diagnosis generates considerable mental and emotional exhaustion, both for him and for his family.[6-8]

In this situation, the most common feelings manifested by affected individuals and their families are anguish, stress and despair, motivated by uncertainty and distress about the disease and its future. The lack of answers about the health condition, its possible worsening, the logistical and bureaucratic challenges to obtain treatment and diagnosis are factors that corroborate the psychoemotional suffering of both the patient and his family, not to mention the social stigma associated with rare diseases.[9]

In Brazil, although genetic testing and post-diagnosis follow-up are offered free of charge by the SUS through the National Policy for Comprehensive Care for People with Rare Diseases (PNAIPDR), many people still face the physical consequences and mental exhaustion resulting from the diagnosis. This is due to numerous factors, such as the population's lack of knowledge about these policies and genetic conditions, and there is also the difficulty of access to specialized centers for rare diseases, concentrated mainly in the South and Southeast regions of the country, which forces citizens to migrate in search of adequate care. In addition, the misinformation of many health professionals about rare genetic diseases makes it difficult for them to diagnose them accurately. These factors, in addition to postponing the treatment of the affected person, impair their quality of life and prolong the impairment of their health.[6,8,10]

As for the social stigma faced by those affected, social exclusion and ableism stand out. These prejudices are aggravated when the condition severely affects the individual's phenotype or motor, neurological or behavioral skills, as they evidence their condition. Thus, cases of bullying against students with genetic conditions in schools are not rare, forcing them to migrate to special institutions, due to the lack of an adequate inclusion program, even if they have the mental and physical condition to follow classes in regular schools. Such prejudice extends to the professional sphere, with situations occurring in which differentiated treatments, whose objective is to help the patient, become ableist when they show low expectations regarding the patient's abilities or potential, or even when the necessary help does not exist due to the negligence of the leaders or those responsible. Thus, by being seen as inferior and incapable by society and having their disease as a source of prejudice and discrimination, those affected by rare genetic diseases feel helpless and disillusioned, which negatively affects their health-disease process.[11,12]

Therefore, aiming at effective treatment, improvement in the quality of life of carriers of rare genetic diseases, and the optimization of the search for diagnosis, it is necessary to overcome logistical and infrastructural clashes and social and medical misinformation. However, there is also a demand for psychological attention to treat the traumas, stress and sadness generated during the odyssey traveled towards adequate medical care, characterized by challenges of social inclusion and physical and mental exhaustion.

Thus, this study aimed to review the psychoemotional impact suffered by those affected by rare genetic diseases during the health-disease process, highlighting the importance of considering these aspects so that the integral treatment, symptomatic aspects of the disease and its mental and emotional consequences, are provided to these individuals.

METHOD

This is a narrative review of the literature consisting of review articles and case reports from 2000 to 2024, in Portuguese and English. In the search for articles pertinent to the theme and appropriate to the study, the Scielo, PubMed, Google Scholar and Capes Periódicos databases were consulted, through the application of the following descriptors: rare diseases, genetic diseases, psychological stress, treatment and diagnosis, resulting in 20 articles that were used in this study.

DISCUSSION

Genetic diseases

Genetic diseases can be inherited or result from de novo mutations, and can be congenital or developed throughout the individual's life. Such clinical conditions manifest themselves as physical, mental or sensory defects, and, therefore, tend to alter the quality of life of the affected person and bring daily complications to him. These diseases can be classified as monogenic, chromosomal, mitochondrial, complex,

and multifactorial.[1,3,5,13]

About 80% of genetic diseases are hereditary, and the risk of a child being born with a genetic alteration is higher when the family has a family history of a genetic disorder, when the parents already have a child with the characteristic or in consanguineous unions.[2,7]

These conditions can also arise due to environmental influences, as some factors related to the quality of life of individuals can contribute to the occurrence of genetic mutations, especially somatic ones. For example, contact with substances that are harmful to health, such as radiation, chemotherapy drugs, and chemical pollutants, increases the risk of spontaneous mutations in genes housekeeping, that is, maintenance and control of the organism as a whole. Therefore, it is important to maintain a good quality of life for the body to function well, and to prevent not only genetic diseases, but also acquired ones.[14]

The WHO (World Health Organization) estimates that the number of individuals affected by a rare genetic disease is 1.3 people per 2,000, which would correspond to approximately 300 million people in the world, with between 6 and 7 thousand different genetic diseases.[8] According to data from the Ministry of Health, in Brazil this number is about 13 million people affected. Still, only 10% of these diseases have specific treatment, often at a high cost.[3,7]

Although there is a large number of people affected by rare genetic diseases, most of the scientific literature concentrates studies on approximately 113 diseases, considering that these conditions still receive little attention in the psychosocial sphere, with limited literature on their psychosocial influence on the individual's life.[7,15]

Difficulties in diagnosing rare genetic diseases

Diagnosing genetic diseases is challenging for the medical field, as it is often difficult to know which condition is affecting the person, given that some of its symptoms are similar to the symptoms of common diseases. Genetic consultations with specialists, prenatal tests, and specific genetic tests on the patient and their family members, affected or not, can help prevent, understand, and identify possible genetic diseases. If pathogenic and/or likely pathogenic variants are in genes that encode proteins and enzymes involved in important biochemical pathways or lead to changes in brain structure, ancillary laboratory and imaging tests can be performed at diagnosis. However, if these are not available, the diagnosis ends up being completely clinical, without confirmation through complementary tests.[2,3] Genetic counseling is another practice that can help and inform people about genetic diseases. For this, professionals need adequate information to guide patients about the risks of recurrence and how these diseases are transmitted. This consultation is usually indicated for people who have a history of neurological or degenerative diseases, a personal or family history of cancer and in cases of repeated miscarriage and infertility.[1]

In addition, preimplantation genetic diagnosis can also be a way to diagnose genetic diseases in cases of pregnancies with risk factors, such as advanced maternal age, family history of a genetic disease or consanguinity. This test is performed on embryos generated for in vitro fertilization before they are implanted in the uterus, making it possible to select the most viable embryos without mutations in genes that could compromise the health of the fetus. Thus, it is a technique that allows the diagnosis of various genetic diseases, but its cost is very high, making it inaccessible to a large portion of the population. In Brazil, this test is regulated by the Federal Council of Medicine, but there are still debates about its ethical implications, due to the disposal of embryos.[16,17]

When the disease is rare, several challenges arise due to the lack or difficulty of access to specialized professionals, resources, treatment and information. In these situations, the most frequent feelings in families are that of impotence, anguish and revolt. Also, the misinformation and frustration generated create mistaken expectations about the disease, which interferes with adequate adherence to treatment and the search for diagnosis.[8] On the path to diagnosis, excessive and unnecessary tests are often requested, as well as incorrect diagnoses and inefficient treatment are provided, generating even more stress for the patient and their families.[10]

Thus, the delay in obtaining the diagnosis generates strong feelings of despair, stress and confusion, which requires psychological treatment from both the patient and their families.[9]

In these cases where the diagnosis takes a long time to be reached, or even is not, the affected person tends to lose hope in his health and resigns himself to the fact that his situation may not change. The main impacts suffered by patients can be divided into psychological impacts, social implications, and functional impacts, which worsen as diagnosis and treatment become delayed.[10]

In Brazil, there are no specialized services in genetic health in all parts of the territory, forcing those living in smaller cities to travel to large centers to obtain access to specialists and a better medical-hospital structure for treatment. For those individuals without human and financial resources, such a displacement is usually unfeasible and, when executed, time-consuming and loaded with logistical challenges and financial difficulties. In the absence of adequate professionals, the diagnosis is often mistaken or the disease is neglected. In addition, due to the long waiting time, contact with specialists is often made after the damage caused by the disease is already irreversible or when it is in an advanced stage, generating a worse prognosis.[7,8]

Challenges in the treatment of rare genetic diseases

The treatments of genetic diseases vary according to their manifestations. However, there are drugs,

especially intended for the treatment and/or control of certain rare genetic diseases, whose costs are high and are not yet included in the list of exceptional drugs through judicial measures, making it difficult for the general population to access them. Also, rare genetic diseases usually require costly exams and numerous consultations with different professionals, generating a long journey from diagnosis to treatment.[6]

Therefore, the treatment of rare genetic diseases is a challenge aggravated by practical-relational and bureaucratic-institutional problems.[3] When diseases are rare, high-cost drugs are associated with orphan drugs, so called, because they are usually not developed by pharmaceutical industries due to economic reasons and low demand and profit potential. In developing or underdeveloped countries, even if there are people with rare genetic conditions, many of these people are unable to afford the drugs due to their high cost. This causes many patients to resort to judicialization as a way to gain access to them. However, there are uncertainties as to whether or not the medication will be released. Many doctors do not consider judicialization the best option and claim that it stigmatizes patients as "a problem patient for the State".[3,18]

In Brazil, aiming to solve this problem, there is the National Policy for Comprehensive Care for People with Rare Diseases (PNAIPDR), which provides funding for reference centers so that genetic tests can be carried out in them and that they can offer medicines and genetic counseling to people who need them, free of charge, through the SUS. Its guidelines provide primary health care (PHC) actions, covering early diagnosis and genetic mapping for people with risk factors and suspicious situations, as well as post-diagnosis clinical follow-up and care when necessary.[8] However, not all those affected can access this policy, which may not be as effective in practice as in theory.

In addition, further raising costs, the treatment of a genetic condition usually requires the monitoring of professionals other than the doctor, such as physiotherapists, speech therapists and psychologists, to try to alleviate the symptoms of the disease and slow its progress.

Another problem that hinders the diagnosis and treatment of genetic diseases is the fact that in Brazil there are few geneticists. Thus, the number of professionals is insufficient and most patients do not receive adequate attention and care. It is also noteworthy that most genetics services are concentrated in the South and Southeast regions of the country. This centralization of services causes the migration of many people to different regions in search of treatment. Often these families end up having to quit their jobs and reorganize their life in the city due to the treatment of the affected family member.[8]

A study funded by the Wellcome Trust in Brazil, a British institution that promotes scientific research in several areas, showed that patients often face a long and tortuous path to reach the final diagnosis. The health professionals interviewed during the study pointed out the lack of information about rare genetic diseases on the part of primary care professionals with a barrier to diagnosis. Due to this factor, many professionals feel insecure in prescribing medications, fearing the worsening of the disease. It is noteworthy that the explanation about the disease tends to help the family in the information process, while misinformation impairs adherence to treatment and corroborates the patient's social isolation, due to insecurities.[6] This study also showed that the lack of access to the services of specialists in SUS genetics and the itinerary taken to reach the final diagnosis of the disease, consisting of several tests and many consultations, corroborates erroneous and late diagnoses, causing the disease to advance due to lack of treatment or inadequate treatments. These consultations are often carried out in the private network due to lack of option, generating several extra costs, which can harm people's routines, especially the low-income population. In addition, even though SUS guidelines provide for multiprofessional care for those affected by genetic diseases, access to these professionals remains precarious and there is a long wait, due to the lack of material and human resources.[6]

Those patients who have experienced late diagnosis are affected by great psychological trauma. This is due to the exhaustion caused by constant consultations with different specialists, who do not reach effective conclusions or guide inappropriate treatments, further damaging their health. Thus, feelings of frustration, anxiety, low self-esteem, shame about their condition (especially in cases where the symptoms of the disease affect the physical appearance of the affected person) and insecurity are very present in their lives. These, without a diagnosis, only know that they are sick, which tends to generate a pessimistic view of life and impairs their long-term planning. Such feelings also negatively affect the social interactions of those affected, making it difficult to maintain healthy relationships and access professional and educational opportunities. Also, with the delay in diagnosis, there is an increase in the lack of credibility in medicine; Thus, several individuals and/or family members turn to alternative sources and without scientifically proven information in search of answers.[10]

Impact of genetic diseases on the daily lives of patients and their guardians

With rare genetic diseases, family members deal with new challenges when faced with treatment and lifestyle changes due to the disease. Those affected need treatments and interventions throughout their lives. This affects their relationships with friends and family, causes the deprivation of certain activities as a result of complications of the disease or the lack of time generated by medical commitments, which corroborates the suffering of mental health. Adaptation is made even more difficult in cases where

the disease causes pain, high risk of life, sensory and/or motor losses or when it includes invasive treatments that strongly affect their routine.[11]

Doctors usually see the mother figure as the protagonist of the pain of having a child who suffers from some genetic disease; the mothers of these children are idealized as people who put their lives aside to dedicate themselves to these children. In this way, many responsibilities are directed to the mother, and the woman may end up feeling pressured when having to deal with everything related to her children. In addition, this material and affective overload can end up generating tensions and emotional and physical problems for her. Another consequence of this exclusive dedication to the affected child is the impossibility of performing various activities, including leisure activities. Depending on the disease, the child needs constant care, and without being able to divide time between work and children, many mothers end up giving up their professional and personal lives, and over time, they may end up suffering physically and emotionally.[10]

Also, after the diagnosis of the disease, although the feeling of relief commonly occurs, many parents blame themselves for their children's diseases, which generates anguish and hinders the health-disease process for the family.[10]

In this perspective, the importance of the doctor informing the family about the condition, forms of transmission and risks of recurrence is emphasized. It is essential for the professional to highlight to the patient and his family that the presence of a genetic disease, even if it is hereditary, is not due to the parents, family members or even the affected person, also emphasizing the existence of other factors that corroborate the development of these diseases.[1]

In cases of high risk of life, families tend to adopt two distinct behaviors: overprotection or negligence. The first is due to the child's perception of fragility and the search to meet all their needs, something that sometimes occurs in an exacerbated way, further limiting their autonomy. The second occurs in an attempt to reduce affective involvement in the event of death, to avoid great suffering.[11]

The invisibility of the patient mentioned above does not only occur in the family sphere, but also in the medical and social sphere. Some professionals may end up having a limited view of the patient by focusing only on their condition and complexity, leaving aside the patient as an individual who needs clarification, has pain and feelings. In addition, the immersion of these individuals in society can be very difficult. There are many limits placed by diseases, whether physical, mental, understanding and the ability to interact socially. Society tends to look at these people differently, as if these individuals were victims of something very bad, leading to a process of discrimination. There are also those whose view of those affected is of inferior people and incapable of performing various jobs, something that emotionally affects both the patient and his family.[12,13]

Still regarding the inclusion of rare disease patients in society, even if they are physically "included" in the communities, they usually remain intellectually segregated. This situation is evident in schools, where the integration of those affected does not occur due to the lack of teacher training and the absence of school support professionals trained in inclusion. Inclusion in most schools is utopian, as the work done by professionals tends more towards ableism, leading to segregation or even exclusion. For this reason, many children with genetic diseases, even with conditions to follow the education in ordinary institutions, go to study in special schools, something that contributes to the feeling of exclusion experienced by those with genetic diseases. Although some children enjoy the time spent in these schools, from a certain age they become aware of the social stigma and the reason for being in that institution. They soon become hesitant about others' views of their school and their medical condition and how it will affect their life in society.[14]

When these people attend normal schools, they are often easy targets for bullying and exclusion, due to the stigma of society-imposed standards of "normality," especially when professionals and classmates do not understand their condition and do not recognize the importance of acceptance and mutual respect. This social isolation is greatly aggravated when the disease generates symptoms that affect the carrier's physical appearance or motor skills, such as wounds or speech difficulties.[11]

Without the support of society in general, religions and cults tend to be a support network for those affected. Todd[14], in 2021, studied the relationship between religions and the behavior of patients, doctors, and families. The values preached can serve as an incentive for the individual to persist in the fight against his disease, for the doctor not to give up on the patient, for the families to continue to support the affected family member and for the others to develop a sense of empathy and compassion. Also according to Todd, another action generated by religion are initiatives to help the sick, such as campaigns to collect donations and funds to pay for treatment. Furthermore, the ideals of valuing life present in various beliefs serve as an encouragement to professionals, patients and society to persist in the fight against diseases and for the appropriate treatment of those affected.[14]

CONCLUSION

Rare genetic diseases have several implications for those affected and their families, with the main impacts being psychological (anxiety, fear, uncertainty), functional (loss of independence, limitations generated by the disease, reduction of academic and professional opportunities) and social (social exclusion, low socialization capacity). These are aggravated when the diagnosis is late, which favors the progression of the disease and the loss of hope of the individual and his family, which generates feelings of resignation, revolt and shame. Thus, it

becomes evident the need not only for the treatment of rare genetic diseases so that their carriers can be inserted into society and overcome their social difficulties, but also for psychological monitoring of patients and their families so that they are able to face the difficulties and challenges arising from the condition and the non-acceptance of the individual by society.

Authors' contributions

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