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Broca's area concept doesn't exist in low grade gliomas – a case series

O conceito de área de Broca não existe em gliomas de baixo grau – uma série de casos

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ABSTRACT

Introduction: Broca`s area is a region located in the left inferior frontal gyrus and is classically correlated to language. However, we observe preservation of speech function after tumor resection in this area. Awake surgery with direct brain stimulation is a reliable method to evaluate the functional role in this area.

Objective: To evaluate the Broca´s area function.

Methods: In a series of 69 patients with tumors in eloquent areas, 7 patients with tumors involving Broca´s area undergoing awake surgery with direct brain stimulation between 2007 and 2017 were retrospectively evaluated.

Results: From 7 patients with Broca´s area stimulation, 5 did not show any alteration of speech. One patient, Portuguese native speaker, started to speak in English during the stimulation. The last patient diagnosed with glioblastoma already had a partial speech deficit, and showed a complete interruption of speech during the stimulation of Broca`s area.

Conclusions: Broca`s area does not seem to be crucial for language function in patients with gliomas involving this area, particularly in low-grade gliomas. The direct brain stimulation is a very useful tool to analyze the correlation between anatomy and brain function.

KEYWORDS: Broca´s area; brain mapping; language disorders; glioma, neuroplasticity

RESUMO

Introdução: A áreas de Broca é uma região localizada no giro frontal inferior esquerdo que é classicamente relacionada a linguagem. Porém, observa-se a manutenção da função da fala após a ressecção de gliomas nessa área. A estimulação cerebral direta com o paciente acordado é um método confiável para avaliar o papel funcional dessa região.

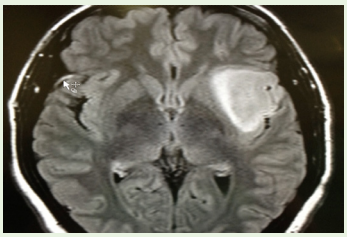
Objetivo: Avaliar a função da área de Broca.

Métodos: De uma série de 69 pacientes com tumores em áreas eloquentes, 7 pacientes com tumores envolvendo a área de Broca e submetidos a cirurgia acordado com estimulação cerebral direta entre 2007 e 2017 foram avaliados retrospectivamente.

Resultados: Dos 7 pacientes que tiveram a área de Broca estimulada, 5 não apresentaram nenhuma alteração na fala. 1 paciente, nativo da língua portuguesa, começou a falar em inglês durante o estímulo. O último paciente, que apresentava um glioblastoma e já tinha déficit parcial de fala, apresentou interrupção completa da fala durante a estimulação da área de Broca.

Conclusões: A área de Broca não parece essencial na função da linguagem em pacientes com gliomas envolvendo essa área, particularmente em gliomas de baixo grau. A estimulação cerebral direta é uma ferramenta muito útil no estudo da correlação entre anatomia e função cerebral.

PALAVRAS-CHAVE: área de Broca, mapeamento encefálico, distúrbios de linguagem, glioma, plasticidade neuronal



Left insular glioma

Central Message

Surgery of glial tumors in eloquente areas, including the region of language and speech, is still a major dilema in neurooncology, especially with regard to the objective of surgery to maximize the extent of resection while preserving or even improving brain functions. This paper presents the experience of neurosurgeons on the theme.

Perspective

The concept studied and proposed by the present article shows us that slow-growing tumors such as low-grade gliomas or high-grade glioma who started being low grade, can be resected in eloquent areas of speech and language, with satisfactory recovery and absence of permanent functional deficits.

INTRODUCTION

Surgery of glial tumors in eloquente areas, including the region of language and speech, is still a major dilema in neurooncology, especially with regard to the objective of surgery to maximize the extent of resection while preserving or even improving brain functions.[1-16]

The purely anatomical knowledge is not enough to predict the eloquence of the different brain regions and to avoid the permanent post-operative deficits in the operated patients, since there is a great anatomofunctional variability of the regional connections between each individual.

Unlike the somatotopic organization of the sensoriomotor cortex, which is relatively static, the location of the cortex responsible for language has considerable variability between individuals.[1] Understand the brain plasticity, combined with advanced brain mapping techniques, allows the safe resection of low-grade gliomas in the eloquent areas of speech and language.[16-19]

The Broca's area is formed by the pars opercularis and triangularis of the inferior frontal gyrus and middle frontal gyrus, which represent the motor projection area for the hand and for the phonation organs.[20,21] Some have included more posterior cortical regions, such as the rostro-ventral precentral gyrus.[22] Others have included an anterior extension that reaches the orbital sufaces.

Injuries in the Broca's area are related to aphasia of expression. These definitions come from a study model based on the study of injuries, mainly ischemic injuries of the central nervous systems.

It is postulated that due to brain plasticity, some slow-growing tumors, such as low-grade gliomas located on or around language areas, functionally shift these areas to brain anatomical regions that classically are not correlated to Broca's area or others classic language areas.[2,3,9,10] This has been observed due to cortical and subcortical stimulation with the patient awake during brain glioma surgery.[10,12,23-28]

The aim of this study was to specify the result of cortical mapping on the Broca's area in our patients, making it possible to indicate surgery on eloquent area, previously considered inoperable; improve the quality of surgical resection according to functional limits; and minimize the risks of permanent postoperative neurological deficits.

METHOD

This study was approved by Research Ethics Committee of Hospital das Clínicas de Porto Alegre with CAAE: 50055015.2.0000.5327.

From a series of 81 patients with eloquent brain tumors operated on by the first author (GRI) between 2007 and 2018, 9 with glioma on the dominant hemisphere localized on or around Broca's area were operated on using awake cortical and subcortical brain mapping. Only patients in which the classical Broca's area was stimulated were considered in this study. Patients with tumors in the motor and premotor areas, parietal lobe and temporal lobe were not included in this series. Likewise, patients with metastases in eloquent areas were also not included.

The first part of the patients was operated on at the Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brasil, and were part of a research project of the postgraduation program in surgery at the Universidade Federal do Rio Grande do Sul, Porto alegre, RS, Brasil. The others were operated on at the Hospital Moinhos de Vento, Porto Alegre, RS, Brasil and in public hospitals where the CEANNE project had been introduced.

We administrated the following pre-operative tests: test of picture naming (D80 test) and Boston Diagnostic Aphasia Examination.[29] Karnofsky Performance Status (KPS) scale was evaluated pre- and pos-operation.

Our parameters of intraoperative cortical and subcortical electrical stimulation were been utilized according the findings of others and based on previous methodology.[9,10,16,30] Patients were asked to say, "this is a ..." before naming each picture in the picturing-naming task. This helps to diferenciate an speech arrest caused by a seizure from a transient language disfunction due to stimulation.[10,31]

Volumetric analysis

Until 2013, we calculated tumor volume using the 3 largest diameters (D1, D2 and D3) of the tumor taken from T2-weighted MR images along the 3 principal anatomical planes. Then we estimated tumor volume using the formula D1 X D2 X D3 / 2.12 The three-to-four-month postoperative volume in those cases with residual tumor was calculated the same way. Since 2014 we are using OsyriX via stored files of MR images in DICOM format (Digital Imaging and Communications in Medicine).[32]

RESULTS

Table shows the data of our series. All tumors were located on the left hemisphere. After 6 months of surgery, no patient showed neurological deficit regarding language or somatosensorial.

TABLE — Data of patients included in the serires (n = 9)

Patient	Gender	Age	Tumor grade	Location	Pre-op volume (cm^3)	Ressection	Broca's area stimulation
1	F	34	II	Left insula	30	100%	Silent
2	F	19	IV	Left temporo-insular	39	100%	Silent
3	F	50	III	Left inferior forntal gyrus	18	Biopsy/ Partial ressection	Language switching
4	F	29	II	Left fronto-insular	41	69%	Silent
5	F	21	III	Left fronto-temporo-insular		63%	Silent
6	M	52	IV	Left insular	35	85	Silent
7	M	39	IV	Left frontal	26	100	Silent
8	M	36	III	Left frontal. Temporo-insular	44	73	Silent
9	F	29	II	Left frontal. Temporo-insular	39	52	Silent

Cases 4,5,8 and 9 were insular gliomas encasing the lenticulostriates arteries. In theses cases the medial limit of the resection was not the subcortical mapping, but instead, was the visualization of the lenticulostrate arteries (Figures 1, 2 and 3).

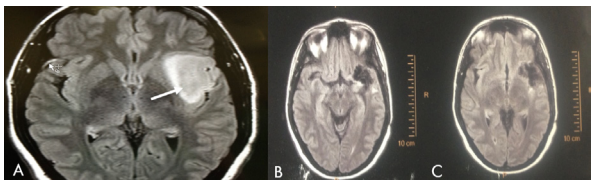


FIGURE 1 — This figure shows case 1: A) 34- years-old lady who had a refractory epilepsy due to a left insular glioma (preoperative FLAIR MRI)(White arrow). She was operated on in other hospital where a biopsy was performed. During our procedure, mapping of the Broca's area was silent. The tumor coud be totally resect by a transylvian approach (Postoperativer FLAIR MRI six-months afer surgery)(B and C). A corticectomy was not necessary to expose the tumor. The patient had no postoperative deficits and is now seizure-free (Engel 1)

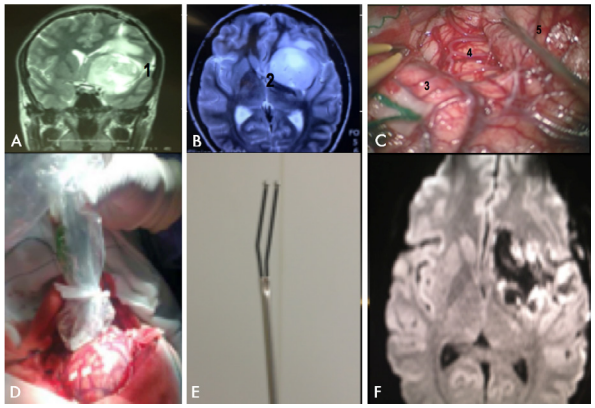


FIGURE 2 — This figure shows case 2, referring to 19-year-old female with uncinate seizures resistant to anti-epileptical drug treatment showing: A and B) coronal T2 axial MRI showing left insular tumor, were microsurgical resection of the tumor was chosen using a transilvian approach with cortical and subcortical mapping with an awake patient; C) intra-operative image showing wide dissection of the silvian fissure and visualization of the stretched M2 branches over the insula due to the (central) tumor, being in 1 Silvian fissure, in 2 genu of the inner capsule, in 3 inferior frontal gyrus, in 4 insula, and 5 superior temporal gyrus; D) intraoperative ultrasound was useful to locate the relationship of the tumor to the eloquent cortex; E) bipolar stimulator used for cortical and subcortical mapping; F) FLAIR MRI in the first 24 h after surgery showing tumor resection without postoperative deficits in patient´s activity. (Histology: GBM with PNET like componenet (WHO 2016).

DISCUSSION

The first experiment to identify the location of brain functions through cortical excitability were carried out in the 19th century using stimulation of the anterior cortex in dogs, evoking contralateral movements and identifying the cross laterality of brain functions. In 1917, the motor cortex was somatotopically mapped for the first time still in animal studies.[13,31] In the late 19th century, several surgeons began to use cortical direct electrical stimulation to perform cortical mapping in humans, highlighting the work of Horsley who did the first example of corticectomy for excision of an epileptogenic area identified by cortical stimulation.[33]

The first studies that described brain functions related to speech and language originated with Paul Broca (1861) and Carl Wernicke (1874), who demonstrated the anatomical location of these functions in the brain

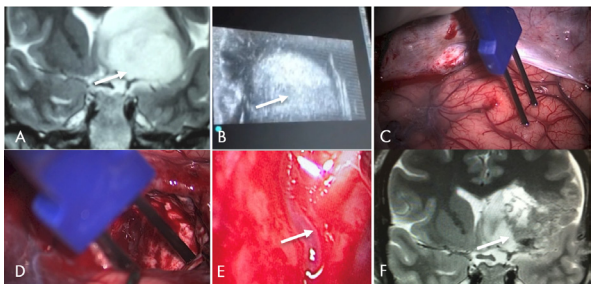


FIGURE 3 — This figure shows case 5: A) pre-operative coronal T2 weighted MRI sequence showing a left insular tumor involving the area were the lenticulostriates arteries are supposed to be located (white arrow); B) intraoperative transcortical Doppler localized tumor borders in real time (white arrow); C) cortical brain mapping showed that middle and inferior left frontal gyri were silent, and classical Broca's area was resected in order to a transcortical approach is performed; D) the subcortical mapping was performed; E) microscope intraoperative view of the lenticulostriate artery (white arrow) which proves the medial limit of the resection in this case was based on the position of theses arteries and not in the subcortical mapping; F) postoperative coronal T2 weighted MRI sequence showing resetion of the lateral part of the insular glioma, leaving the lenticulostriate arteries behind (white arrow). There were no deficits in the postoperative.

by relating the inferior frontal gyrus to the speech articulation and the posterior temporal lobe with language understanding. Dejerine (1906) and Marie (1906) reformulated the previous theory, identifying the superior temporal gyrus and the inferior parietal lobe as the language area's comprehension. With the advance of neuroanesthesia and the emergence of craniotomies in the awake patient, Penfield was the pioneer in more precisely mapping the organization of speech and language areas through direct cortical electrical stimulation. In his study, it was observed that injuries or stimuli close to the posterior portion of the inferior frontal lobe affected the speech motor components; close to the temporo-parieto-occiptal junction affected reading and writing; and close to the posterior region of the superior temporal lobe caused difficulty in understanding language, thus rejecting the idea of a static location between the connections of speech and language, and proposing a dynamic connection, in which, a network of cortical areas interconnect and could compensate deficits caused by injuries in these areas.

Recently, with the evolution of modern anesthesia techniques with awake patients and the use of direct cerebral subcortical electrical stimulation, there has been a further refinement in the location of language areas. The mapping of fiber tracts in white matter was crucial to avoid permanent deficits related to speech and language functions. Duffau et al.[14] reported the first intraoperative mapping capable to identify the subcortical tracts related to language and speech, including the subcalous fasciculus (stimulation resulted in anomia and reduced speech fluency) and the arcuate fasciculus (conduction aphasia). Their study was carried out in patients with low grade gliomas, with the aid of direct subcortical electrical stimulation, and no patient had a postoperative deficit. Thereafter, a new understand

of the organization of these connections was recognized, being interconnected (hodotopia - Organization of the central nervous system consisting of networks connected in parallel) and becoming dynamic (able to compensate each other in case of injury) due to adaptive plasticity , which is why the resection of eloquent brain regions such as Broca's area can be performed without induce neurological deficits.[15] The hodotopic model developed through anatomical correlation with electrical stimulation shows that brain processing is not simply the sum of several networks working independently, however by the integration of overlapping and parallel connections.

This creates a static paradigma organization of brain functions, purely anatomical, known until then and initiated by the studies of Broca and Wernicke, which does not consider a brain's ability to compensate for any damage caused in eloquent áreas.

Numerous studies of functional neuroimage in patients with low-grade gliomas have recently demonstrated that there is a progressive redistribution of eloquent areas, justifying why these patients sometimes have normal neurological examination or minimal deficits.[1] In patients with glioma located in the Broca's area without afasia, functional MRI demonstrated activation of adjacent regions in the inferior left frontal cortex, superior temporal gyrus, left putamen and contralateral hemisphere.[34]

The goal of low-grade glioma surgery is to achieve maximum tumor resection, avoiding or minimizing the risk of neurological sequelae for the patient.[35] Radical surgery removal of low grade glioma when possible, currently appears to be the first treatment to influence the natural history of this lesion.[36] However, due to the frequent localization of supratentorial gliomas in eloquent areas or their surroundings, and their infiltrative characteristic, many studies considered that the chances of have a total resection were low, due to the high risks of post-operative deficits, reporting rates of severe and permanent sequelae from 13% to 27.5% after surgery.[37,38]

Recent advances in identifying methods from these interconnections are emerging with brain mapping that permits to study the functional organization of the brain for each patient, then to tailor the ressection according to both oncologic and cortico-subcortical functional bounderies.[15]

In the past decade, non-invasive preoperative techniques including functional MRI, positron emission tomography (PET) and electroencephalography allowed the cortical mapping of the brain in general. However, the reliability of these methods was low (82-100% sensitivity to identify sensorimotor areas and 66% to 100% for language areas), not allowing to differentiate brain regions responsible for essential functions.[24]

To optimize the benefit and reduce the risks of surgery, intraoperative electrophysiological techniques (direct electrical stimulation - cortical-subcortical mapping, especially in awake patients) have been developed in the last decade, allowing the identification of functional cortical areas and subcortical connections during surgery and guiding tumor resection according to individual functional limits. Identify and preserve not only eloquent cortical sites, but also functional pathways indispensable for language function, including parenchymal regions of cortical grey substance and white matter fibers.[15]

This is the gold standard method for identifying these regions in glioma's surgery localizated in eloquent areas.

If the tracts related to the functions of language and speech are found within the tumor, the chance of total resection is limited; however, if distributed around the lesion, in remote areas of the ipsilateral hemisphere or contralateral homologous regions, there is a great chance of having a total resection of the tumor, even with the appearance of an immediate transient deficit, which recovers in about a week or months.[16,25,26] Cortical-subcortical direct electrical stimulation (DES) allows the mapping of language functions, studying anatomical-functional connections by stimulating white matter tracts during surgery.[27,35] DES is an accurate, reliable and safe method .

Consequently, any speech and language disorder induced by intraoperative stimulation, must be recognized and interrupt the resection at the stimulated site. Stimulation has elicited transient symptoms classicaly observed in conduction aphasia, associating phonemic paraphasia and repetition disorders.[27] In gliomas located in or near Broca's area, cortical-subcortical electrical stimulation can identify the function of speech being compensated in adjacent regions – left ventral premotor cortex, middle frontal gyrus and pars orbitaris or areas around the supramarginal gyrus. Some studies even show the compensation of the contralateral hemisphere in some cases of low-grade glioma located in the Broca's area.[17,28,39] In patients with low-grade gliomas in eloquent areas who were operated with the aid of cortical-subcortical electrical stimulation, more than 95% of patients showed recovery from neurological deficits symptoms after 3 months, and absence of tumor on postoperative control MRI of 62% compared to 35% in those who were not operated with the aid of cortical electrical stimulation.[18,35] A significant decrease of seizures in 80% of patients with preoperative chronic epilepsy wal also observed.[20]

It is importante to understand that direct eletrical stimulation is a complementary method offering functional data that cannot be provided using the other techniques. The potential for brain plasticity allows us to understand that when the first surgery to remove the glioma is incomplete due to the detection of eloquent areas in the regions where the tumor is located, a new remodeling of these areas may occur, allowing a new resection of the lesion.[40]

Most of our patients had insular gliomas with no involvement of the left frontal inferior gyrus. In all these cases the mapping on classical the Broca's area was silent. Resection of Insular gliomas is historically considered very dangerous.[11,41-44] Anatomy of the posterior part of the lateral sulcus (sylvian fissure) is covered by several branches of the middle cerebral artery and its perfurators branches. We experienced transylvian for

insular glioma resection with good results and great resections with smaller tumors (Yasargil classification 3A and 3B). On the other hand, a transcortical approach is more suitable to achieve bigger resections and less risky. At least in our experience.

One interesting finding involved our patient number 3, a physician, Portuguese native-speaker, who spoke also English and Spanich. She had a tumor located at the inferior frontal gyrus, and developed language switching during Broca's area mapping. The patient switch language from the native Portuguese to English. Due to this we performed a partial resection in other to avoid any language disability.

Cortical and subcortical language organization in bilingual patients with epilepsy or brain tumors has been studied previously.[19,43] Localization of speech is particulary problematic in patients speaking more than one language. The term bilingual refers to all those people whoe use two or more languages or dialects in their everyday lives.[40,45-51]

It is recommended that in bilingual patients a multiple intra-operative mapping should be performed for all the languages the patients if fluent for. Language testing have to be performed at both cortical and subcortical level, to improve quality of resection and maximally preserve the functional language integrity, avoiding postoperative dysphasia. Multiple separates sites essential for naming can be identifield in the cortex immediately around or over the eloquent areas. These findings stress the importance of the intra-operative practice of eletrical direct stimulation mapping of all languages fluently spoken by a patient in order to maximally preserve functional integrity.[40,45]

CONCLUSION

The concept studied and proposed by the present article shows us that slow-growing tumors such as low-grade gliomas or high-grade glioma who started being low grade, can be resected in eloquent areas of speech and language, with satisfactory recovery and absence of permanent functional deficits.

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