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Research

Tumors of Oligodendroglial Origin, Results of a Five-Year Study

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Abstract

Objective: Oligodendrogliomas are intracranial tumors that represent between 5 to 25 % of gliomas in adults. This study reviews the results of treatment in patients with oligodendrogliomas treated at "Hermanos Ameijeiras" Hospital between January 2015 and December 2020.

Methods: We made an observational, descriptive and retrospective study type cohort in a series of 31 patients with oligodendroglioma treated at "Hermanos Ameijeiras" Hospital.

Results: Predominate male patients with ages between 41 to 60 years (55%), with clinical presentation of seizures in 71% and frontal location in 52%. Total surgical resection was performed in 84% of patient, which supported by adjunctive treatment, achieved total regression of disease in 71 % of patients and postoperative improvement in 100% of the patients according to the Karnofsky functional scale.

Conclusions: Oligodendroglia tumors are gliomas with their own imaging, histological and genetic characteristics. Combination of the different therapeutic modalities has an important role in the control of the disease and its survival, associated with a better neurofunctional state of the patient in the pre-surgical and post-surgical period.

***Keywords:** glioma, oligodendroglioma, nervous system, tumors*

Introduction

The oligodendrocyte, as recognized by Robertson in 1900, is part of the neuroglial cell family and is found predominantly in the white matter of the central nervous system. Oligodendrogliomas are intracranial tumors that represent 5-25% of all gliomas, 5-10% of all primary intracranial neoplasms, 3% of gliomas in children 0-14 years of age, and 5% of children 15 years of age. to 19 years. A worldwide prevalence of 1/300,000 inhabitants is estimated, with a peak incidence between 35 and 45 years of age. [1, 2] Most of the large series show a predominance by the male sex. With the update of the WHO classification of central nervous system (CNS) tumors in 2016, the diagnosis of oligodendroglioma is made by identifying a diffuse infiltrating glioma with IDH (Isocitrate dehydrogenase) mutation and 1p19q codeletion, however in some countries or regional centers molecular markers are unavailable or equivocal. In such cases, the diagnosis reverts only to histological features and is termed Not Otherwise Specified (NOS)[3].

The therapeutic options include observation, surgery, radiotherapy, chemotherapy and immunotherapy, so that based on these, a treatment process is carried out that is more than 90% multimodal.

Material and Method

An observational, descriptive, retrospective cohort study was carried out on patients diagnosed with oligodendroglioma, treated at the "Hermanos Ameijeiras" Hospital, from January 2015 to December 2020, who met the following criteria:

- Patients with pathological diagnosis of oligodendroglioma.
- That they have presented clinical and imaging follow-up in said institution.
- Patients older than 18 years.

All patients were included in the care protocol for oligodendroglial tumors approved at the institution where the study was carried out. The following diagram reflects the behavior followed before each one of the patients[4].

Results

A total of 31 patients were studied, with a predominance of males between the ages of 41 and 60 in 55%, with symptoms of seizures in 71% of the cases and topographic location in the frontal lobe in half of the sample (n =16) 52%; **Table 1.**

Table 1. Distribution of the sample according to demographic and clinical variables and topographic location of the tumor.

Variables	Frequency	Percent
Age		
• (18-40 years)	11	35
• (41-60 years)	17	55
• (más de 60 years)	3	10
Gender (Male)	21	68
Clinical Presentation		
• Headache	18	58
• Intracranial Hypertension (IHS) Syndrome	3	10
• Motor Deficit Syndrome	9	29
• Síndrome convulsivo	22	71
Topographic location		
• Frontal	16	52
• Parietal	9	29
• Temporal	4	13
• Multilobe	2	6

IHS: Intracranial Hypertension.

Table 2. Shows the presence of imaging calcifications in a high percentage of the sample (87%), with a predominance of low-grade tumors in pathological studies that underwent total surgical resection (84%).

Table 2. Distribution according to imaging characteristics, pathology results, therapeutic modality and grading on the Karnofsky Functional Scale (KFS).

Variables	Frequency	Percent
Imaging characteristics		
• Density (CT) mixed.	21	67
• Intensity (MRI) mixed T1-T2 sequence	19	61
• Calcifications		
	27	87
Histology		
• Oligodendroglioma II	22	71
• Oligodendroglioma III	4	13
• Oligoastrocitoma II	2	6
• Oligoastrocitoma III	3	10
Therapeutic modality		
Resection:		
Total	26	84
Partial	4	13
Biopsy	1	3
• Chemotherapy	7	23
• Radiotherapy	28	90
Karnofsky Functional Scale		
• KFS pre -operation (80 or more points)	28	90
• KFS post -operation (80 or more points)	31	100

CT: computerized axial tomography, **MRI:** magnetic resonance imaging, **T1:** T1-weighted magnetic resonance image, **T2:** T2-weighted magnetic resonance image.

Control of the disease according to the RANO [5] criteria is shown in Table 3, where total regression was achieved in 71% (n= 22) of the patients.

Table 3: Control of the disease at five years according to RANO criteria.

Variable	Disease Control	
	Frequency	Percent
Full Regression	22	71
Partial Regression	2	6
Stable Disease Condition	4	13
Disease progression	3	10
Total	**31**	**100**

Discussion

In Cuba, there are few reports about the clinical, imaging and pathological characteristics of oligodendroglioma, as well as the therapeutic results.

In the present series, a total of 31 patients were studied, predominantly those between 41 and 60 years of age in 55% and with an average age of 45.4 years, which coincides with other series reported by Mahsa6, Goel2, Nielsen7 and Achey8. It was also observed that there was a 68% predominance of the male sex in a 2:1 ratio over the female sex, which coincides with what was reported in the reviewed literature[1, 2, 7, 8] and [9].

The characteristics of the infiltrative growth as well as the predilection for frontal location of these tumors leads them to present a high risk of seizures as a form of clinical presentation. Studies by Shibahara10 and Siegal[11] show that headache and seizures are the most frequent symptoms in these patients in addition to motor defects, the latter being found above all in those patients with high-grade oligodendroglial tumors according to the WHO. Our series showed similarity with these studies, headache manifested in 58% of patients and seizures in 71%. Most authors consider that the clinical presentation with seizures is a sign of good prognosis. Likewise, the absence of neurological focality and headache (as a sign of intracranial hypertension) at the time of diagnosis is related to greater survival compared to those patients with neurological deficits[7, 9, 10] and[11].

Oligodendrogliomas are tumors that preferentially affect adults and the majority are located in the cerebral hemispheres[12]. The series show that the frontal lobe is more affected; for example, in Mahsa's series6 of 182 patients, 29.1% were in the frontal lobe, followed by the parietal lobe in 17%, and the least commonly affected site was the brain stem in 2.2%. Zlatescu et al.[13] observed in their study of 64 cases that the tumor genotype was closely related to the tumor location, thus anaplastic oligodendrogliomas located in the frontal, parietal, and occipital lobe were more likely to suffer deletion 1p and 19q than tumors located in the temporal lobe, insula and diencephalon. Our study coincides with the series reviewed, observing the preferred location for the frontal lobe in 52% of the cases, followed by the parietal and temporal in 29 and 13% respectively, while only 6% multilobar location.

Imaging studies are of notable importance since the presence of calcifications, the low contrast uptake of the lesion and the topographic location make us suspect this type of glioma. In the Christine[14] series, the mixed imaging pattern of densities and intensities in CT and MRI respectively was the most frequent, which was related to the fact of the presence of calcifications and cysts in this type of lesions. Calcifications were associated with a good prognostic sign [2, 5, 15]. In our series, the presence of calcifications was reported in 87% of the cases and the presence of mixed density was observed on CT in 67% of the patients. and mixed intensity in MRI in 61%, so our results do not differ from the rest of the reviewed series.

Oligodendrogliomas according to the current 2016 WHO classification present unique genetic characteristics, mainly with the molecular study to find out if there is codeletion of 1p 19q and the IDH mutation, despite the fact that the country does not have studies of genetic biomarkers that would determine the response to chemotherapy and the patient's prognosis, we know that the survival of patients with grade II oligodendrogliomas is greater than grade III oligodendroglioma, as well as survival and prognosis also improves if they do not present any astrocytic component at 2 and 4 years reflected in numerous studies [9,13,16] . Surgical resection was the first line of treatment in the therapy of oligodendroglial lineage tumors associated with a high survival rate. The extension of the surgery constitutes an index of great impact on the quality and prognosis of survival of patients, complete resection is the indicator of greater survival par excellence. Shaw[17] reported a retrospective analysis of 82 patients comparing survival between patients who underwent total and subtotal resection where a survival of 12.6 years and 4.3 years, respectively, was observed. Johannesen et al.[18] reported a survival of 7.3 years after total resection and 6.4 years after performing a biopsy, while in the series by Snyder and other authors19 they presented a comparison of patients who underwent more than 90% and less of 90% of surgical resection appreciating that at 5 years there was a survival of 90% and 87% respectively between both groups with a disease-free period of 62% in the first and 42% in the second group. In our series it was evidenced that the total sample (n=31) underwent surgery, of which 84% (n=26) underwent total resection of the tumor, 13% (n=4) received subtotal resection mainly due to the proximity to eloquent areas despite the support of the neuronavigator, tractography and neurophysiological studies; A single patient underwent a biopsy which presented a left temporomesial location. Given the difficulty for complete surgical resection in many cases and the reduction in the disease-free period in subtotal resections, neoadjuvant radiotherapy and chemotherapy play a fundamental role in the local control of this condition. Since 1990, radiotherapy has represented a fundamental pillar in treatment, retrospective and prospective randomized studies show it as a strong basis for starting postoperative therapy in patients with recurrent and anaplastic oligodendrogliomas20.

However, there are no satisfactory results with high doses of radiotherapy of 54 to 60 Gy, fractional doses of 1.8 to 2 gray in 30 to 33 sessions are recommended, which show a higher survival rate[21]. The advent of radiotherapy made up of images allowed drawing the lesion more accurately and avoiding undesirable effects due to its toxicity, especially hematological. Rusthoven et al.[22] did not report an increase in survival with radiotherapy treatment; on the contrary, a decrease in survival was observed with patients who underwent surgery and radiotherapy compared to those who underwent surgery alone (60 and 78 months of survival, respectively), while Van den Bent and other authors[5] observed that early initiation of radiotherapy in patients with recurrent oligodendrogliomas increased survival and their survival. The role of chemotherapy in this condition has always been controversial. Studies have observed a better response in patients with codeletions of chromosomes 1p/19q. The high sensitivity of gliomas to nitrosureas, such as procarbazine, is well known. , lomustine and vincristine (PCV). Retrospective randomized studies show that anaplastic oligodendroglioma with 1p/19q codeletion benefits from the use of PCV, but this is not the case for those who did not present this codeletion [5, 20.] Another extremely important aspect is the methylation of the methylguanine methyltransferase (MGMT) promoter.) as a direct indicator of response to chemotherapy; Being methylated, it presents a disease-free time of 70 months compared to unmethylated ones with only 16 months[5]. Since 2011, temozolamide (TMZ) with the most recent studies by Lassman[23] and Speirs[16] has been used more frequently than PCV with longer survival, less myelotoxicity, and better tolerability. Speirs[16] in his series of 59 patients compared the use of radiotherapy with TMZ in patients with codeletion 1p/19q and those without codeletion, which yielded a result of 91% survival at 5 years with codeletion and 68 % for those who do not. In his multicenter study of 62 patients, Ahluwalia[24] demonstrated that the TMZ dose of 150mg/m2 for 5 days for 7 to 8 cycles was more effective than its high dose of 200mg/m2 and standard doses of 75mg/m^2 to 120mg/m^2. . Treatment alternatives with bevacizumab and immunotherapy are still found[25] in their study of 22 patients with recurrent oligodendroglioma, with 1p/19q codeletion and failed alkylating therapy, showing survival with the use of bevacizumab of 6 to 8 months. The studies by Sandmann et al.[26] showed that survival in patients who received treatment with bevacizumab, radiotherapy, and chemotherapy with temozolamide was 10.7 months compared to those who did not receive bevacizumab, which was 7.3 months. Some agents such as the SOX-2 peptide are still under study, with encouraging results in association with TMZ. In our series, 90% (n=28) patients received adjuvant treatment with radiotherapy and 23% (n=7) patients received concurrent radiotherapy and chemotherapy. The most widely used image-conforming radiotherapy was intensity-modulated radiotherapy (IMRT), chemotherapy was performed with the scheme of procarbazine, vincristine and cisplatin (PVC); with a dose of procarbazine 60mg/m2 from 8 to 15, vincristine 1.4mg/m^2 on days 8 and 15, cisplatin 50mg/m2 on the first day; This scheme is repeated every 28 days in 6 cycles, which, added to surgery, achieved a survival rate and disease-free period comparable to the results of the world studies reviewed.

In relation to the control of the disease at five years we were able to observe in our study that there was regression in 77% of the cases, of them 71% total and 6% partial, the disease remained stable in 13% of the patients, which in our opinion is due to a large extent to the resective surgery with the principle of being maximum safe that was offered to patients using novel surgical techniques performed in our service such as surgery through small cerebral ports for deep lesions, supported by stereotaxy or neuronavigation through endoscopic and microscopic magnification, as we know surgery is the factor with the greatest impact on survival and disease control in these patients, as well as the possibility of later receiving therapeutic adjuvant chemotherapy and radiotherapy as part of of a multimodal treatment. In 10% of the cases there was disease progression, which is related to the most aggressive histological forms of tumors, that is, anaplastic, as well as the possibility of molecularly presenting the absence of codeletion of 1p/19q and absence of the mutation. IDH, which, as we know, we cannot verify in our environment due to the impossibility of performing these genetic biomarkers due to lack of resources, in addition to multilobar presentations and deep locations in eloquent areas that are only candidates for biopsy from the point of view of a surgical alternative. Therefore, the best survival and disease-free period occurred in those patients with good prognostic factors such as low histological grade of the tumor, the extension of the resection (maximum and safe), the presence of calcifications in the tumor, the clinical debut with seizures and high preoperative Karnofsky score.

Conclusions

Oligodendroglial tumors constitute gliomas with their own clinical, imaging, histological, and genetic characteristics. The combination of the different therapeutic modalities plays an important role in the control of the disease and in its survival, associated with the good neurofunctional state of the patient in the pre and post-surgical period.

Conflict of Interest

The authors of this paper declare there is no conflict of interest.

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