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The Relationship Between Location and Prognosis in Brain-Stem Tumors

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Abstract: The objective of this study was to establish a correlation between histopathology and radiological characteristics as well as location of brain stem tumors. Results of therapy were also analysed in relation to the radiological characteristics. Forty four patients were evaluated from a clinical and neuroradiological viewpoint (CT and MRI). In 14 of them we ruled out a surgical therapy. However 30 patients with an age ranging from 4 to 62 years were operated on with complete resection in most cases. We attempted to correlate histopathology with the radiological pattern and location of the tumours. The clinical presentation was as follows: symptoms of cranial nerve involvement in 21, cerebellar symptoms in 18 and pyramidal syndrome in 13. Histopathology was obtained by means of stereotactic biopsy in 4 cases and by means of surgical specimens in 26 cases. Tumors were well defined (focal) in 16 cases and diffuse in 14. Complete removal was achieved in 18 cases and partial in 8. Intraoperative neurophysiologic monitoring was carried out in all cases. Most malignant tumors tend to locate in the pons and to be radiologically diffuse. Conversely, benign tumors use to be focal and to locate in the midbrain, medulla and cervicomedullary junction. There is a good correlation between histopathology and the anatomical location of brain-stem tumors. An adequate selection of cases for surgery based on clinicoradiological criteria and the use of intraoperative neurophysiologic monitoring are of help to improve prognosis after surgery in brain stem tumors.

Key words: Brain-stem tumors, histopathology, prognosis

INTRODUCTION

The diagnosis and management of brain stem tumors has improved markedly in the last 30 years owing to the advances in the neuroradiological techniques, intraoperative neurophysiology and surgical techniques aided by ultrasonic aspirator, lasser devices and microscopy. These advances have made it possible to remove tumors considered before inoperable.

In the past brain-stem tumors were regarded as a gloomy chapter in neurosurgery[9]. The first surgical series appeared in the 60s[6,53,58]. In 1969, on the basis of their location and difficult approach, Matson defined these tumors as malignant regardless of histopathology[53]. Before the use of CT all of these tumors were seen as a homogeneous group. Only anecdotal reports of successful surgery and long survival were published[58].

Brain-stem tumors and brain-stem gliomas are terms used indistinctly because gliomas are the most frequent tumor type at this location. In pediatric wards gliomas constitute 90% of the cases[24,28], however many other types of tumors may appear in the brain-stem: meningiomas, lymphomas, metastasis, arachnoid cysts, abscesses and cavernomas[34]. Other reported tumors are hemangioblastomas[40], epidermoid cysts[56] and lipomas[15,62]. Favorable outcomes after surgery became to appear in the 80s[6,25,28,41,63].

Despite the heterogeneous spectrum of the brain-stem tumors histopathology is verified at most in 58% of cases[47]. This may be due to the small quantity of tissue from biopsies or to the inherent difficulty to perform them. For these reasons neuroradiology has a very important role in the initial assessment of the lesions.

From 1980 onwards important advances emerged in the field of neuroradiology, neurophysiology and neurosurgical techniques with many attempts to classify these tumors[15,23,25,27,28,30,40] and based on CT and MRI techniques The main purpose of classifying tumors was to identify those amenable to surgical removal. The use of intraoperative neurophysiologic monitoring (sensory and motor evoked potentials) provides information in real time on the integrity of brain-stem throughout the surgical intervention[20]. The incorporation of modern devices such as surgical microscopy, bayonet

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plaques[26], contact lasser (Nd-YAG)[46] and ultrasonic aspirator (CUSA)[19,42] greatly contributed to refine the surgical techniques.

There are a few reports pointing to a relationship between location and histopathology and prognosis in brain stem tumors. In the experience of Albright *et al*. the prognosis of midbrain tumors was excellent[5]. In the cervicomedullary junction the reported tumours are mostly low-grade gliomas[24,25]. Gomez-Gosalvez *et al*. reported that all of the 8 tectal tumors were benign[38].

The aim of our study is to verify the hypothesis that the location and radiological aspect of tumors correlates to histopathology and prognosis.

PATIENTS AND METHODS

A total of 44 consecutive cases with brain-stem tumor were initially included in the study but histopathology was possible in 30. The mean age was 22 years (range: 4-62 y). All of them underwent CT and MRI of the brain and were followed up. The duration of clinical symptoms before diagnosis ranged from 45 days to 7 years. In 14 cases it was not possible to get histopathological verification. In the remainder histopathology was obtained by means of biopsy in four cases and by the surgical specimen in twenty six. From a neuroradiological viewpoint we evaluated the focal or diffuse aspect of the tumours, the exophytic component and location: mesencephalic, diffuse in the whole brain-stem (midbrain-pontine-medullary), pontine, pontine-medullary, medullary and cervico-medullary. We also studied the correlation to the symptoms leading to the performance of CT and MRI

The surgical intervention was made with the patients semiincorporated and under cardiorespiratory monitoring. Neurophysiologic monitoring included Somatosensory Evoked Potentials and auditive troncular potentials throughout the surgical intervention. We used microsurgical technique and Lasser CO2.

After surgery the patients were followed-up for variable periods of time with postoperative CT and MRI (range: 6 months-two years).

RESULTS AND DISCUSSION

In table 1 are reported the clinical symptoms leading to the diagnosis according to the anatomic location of the tumors in the 30 cases with histopathology. There were 18 men and 12 women. The most frequent initial manifestations were: cranial nerve paresis in 21, cerebellar symptoms in 18 and pyramidal syndrome in 13. Histopathology was established by stereotactic biopsy in 4 cases and by examination of surgical specimens in 26.

In table 1 are also reported the radiological aspect, location and histopathology. CT clearly demonstrated the tumor in 24 cases by showing hypodense areas, contrast enhancement and cystic or necrotic areas. In case 13 (low-grade astrocytoma) CT was unable to detect the lesion although it met on evidence triventricular hydrocephalus. In case 9 (low-grade astrocytoma) CT was negative and it also occurred in cases 12 (pontine malignant neurofibroma), 7 (Meduloblastoma), 15 (lipoma of the medulla) and 16 (ependymoma of the cervicomedullary junction in which only the solid component was seen in the medulla).

MRI was superior to show the lesions and to establish location. The radiological aspect was better distinguished (focal, diffuse and exophytic component) as well. According to table 1 only the pons was the site of development of malignant tumors.

CT-guided satereotactic biopsy was carried out in 4 cases. In 3 of them surgery was dismissed because of the malignancy of lesions in the pons; instead we chose radiotherapy. In the remaining cases a surgical approach was performed based on the benign aspect, exophytic or subependymal growth or cystic areas.

Complete macroscopic resection was achieved in 18 cases and partial in 8. A ventriculoperitoneal shunt was needed in a case of mesencephalic low-grade astrocytoma. The reasons for partial resection were malignancy and diffuse spreading of the tumor in 7 cases and perioperative cardiorespiratory disturbances in one case.

Perioperative neurophysiologic assessment was carried out in all cases and included Somatosensory evoked potentials and auditive troncular potentials; occasionally we used blink reflex and visual evoked potentials. Neurophysiologic monitoring allowed us to observe functional improvement after opening pial tissues in 9 cases (pons and medulla tumors). In one case surgery was stopped due to serious alterations in neurophysiologic monitoring.

Surgery was initially well tolerated. In case 6 (anaplastic astrocytoma) surgery complicated with intracavitary hemorrhage, coma and death after 3 months of surgery. We saw transient sequelae in four patients: cranial nerve dysfunction, ataxia, vertical and horizontal gaze dysfunction and incoercible vomiting (subependymoma of IV ventricle). All of these symptoms resolved completely after a maximum period of 6 months.

The 4 non-operated patients with malignant lesions survive less than one year (3, 5, 6 and 8 months),

Table 1: Location, radiological aspect, histopathology and clinical symptoms in our series of 30 cases with brain-stem tumour.

Case	Location of tumour	Border type	Histopathology	Clinical symptoms leading to diagnosis
1	Pontine-medullary	Well defined, with exophytic component	Mixed-grade astrocytoma with low mitotic index.	Cerebellar ataxia, cranial nerve paresis.
2	Pontine-medullary	Well defined, with exophytic component	Mixed-grade astrocytoma with low mitotic index	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension.
3	Pons	Diffuse	Glioblastoma	Cerebellar ataxia, cranial nerve paresia, pyramidal syndrome
4	Pons	Diffuse	Glioblastoma	Cerebellar ataxia, cranial nerve paresia, pyramidal syndrome
5	Pontine-medullary	Diffuse	Low-grade Astrocytoma	Cerebellar ataxia, cranial nerve paresis.
6	Pontine-medullary	Diffuse, with exophytic component	Anaplastic Astrocytoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension, cervical dystonia
7	Pons	Diffuse, with exophytic component	Meduloblastoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension, pyramidal syndrome
8	Medulla	Well defined	Low-grade Astrocytoma	Hemisensory syndrome, hypotonia.
9	Cervicomedullary	Well defined	Low-grade Astrocytoma	Hemisensory syndrome
10	Pons	Diffuse, with exophytic component	Glioblastoma	Cerebellar ataxia, cranial nerve paresis, pyramidal syndrome
11	Pontine-medullary	Well defined, with exophytic component	Low-grade subependimoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension
12	Pons	Well defined	Malignant Neurofibroma	Cranial nerve paresia
13	Midbrain	Well defined	Low-grade Astrocytoma	Unsteadiness of gait, diplopia
14	Pons	Diffuse, with exophytic component	Metastasis from lung cancer	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension
15	Cervicomedullary	Well defined	Lipoma	Pyramidal syndrome with spasticity and tetraparesis
16	Cervicomedullary	Well defined, with exophytic component	Low-grade ependimoma	Pyramidal syndrome with spasticity and tetraparesis
17	Midbrain and pons	Well defined	Low-grade Astrocytoma	Pyramidal syndrome, intracranial hypertension, Unsteadiness of gait
18	Pontine-medullary	Well defined, with exophytic component	Low-grade Astrocytoma	Cranial nerve paresis
19	Pons, fourth ventricle	Diffuse, with exophytic component	Meduloblastoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension
20	Midbrain, Pontine-medullary	Diffuse	Low-grade Astrocytoma	Cerebellar ataxia, cranial nerve paresis
21	Pontine-medullary	Well defined, with exophytic component	Low-grade Astrocytoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension
22	Midbrain and thalami	Well defined	Low-grade Astrocytoma	Cerebellar ataxia, pyramidal syndrome
23	Midbrain, Pontine-medullary	Diffuse	Low-grade Astrocytoma	Pyramidal syndrome
24	Pontine-medullary	Well defined, with exophytic component	Low-grade Astrocytoma	Pyramidal syndrome, cranial nerve paresis
25	Diffuse brain stem and cerebellum	Diffuse, with exophytic component	Glioblastoma	Pyramidal syndrome, intracranial hypertension, cranial nerve paresis
26	Diffuse brain stem and cerebellum	Diffuse, with c exophytic omponent	Anaplastic Astrocytoma	Cranial nerve paresis
27	Diffuse brain stem and cerebellum	Diffuse	Low-grade Astrocytoma	Cerebellar ataxia, cranial nerve paresis
28	Pontine medullary	Well defined, with exophytic component	Low-grade Astrocytoma	Cerebellar ataxia, cranial nerve paresis, intracranial hypertension
29	cervico-medullary junction	Well defined	Low-grade Astrocytoma	Pyramidal syndrome with spasticity and tetraparesis
30	cervico-medullary junction and cerebellum	Diffuse, with exophytic component	Anaplastic Astrocytoma	Pyramidal syndrome with spasticity and tetraparesis, cerebellar ataxia, cranial nerve paresis

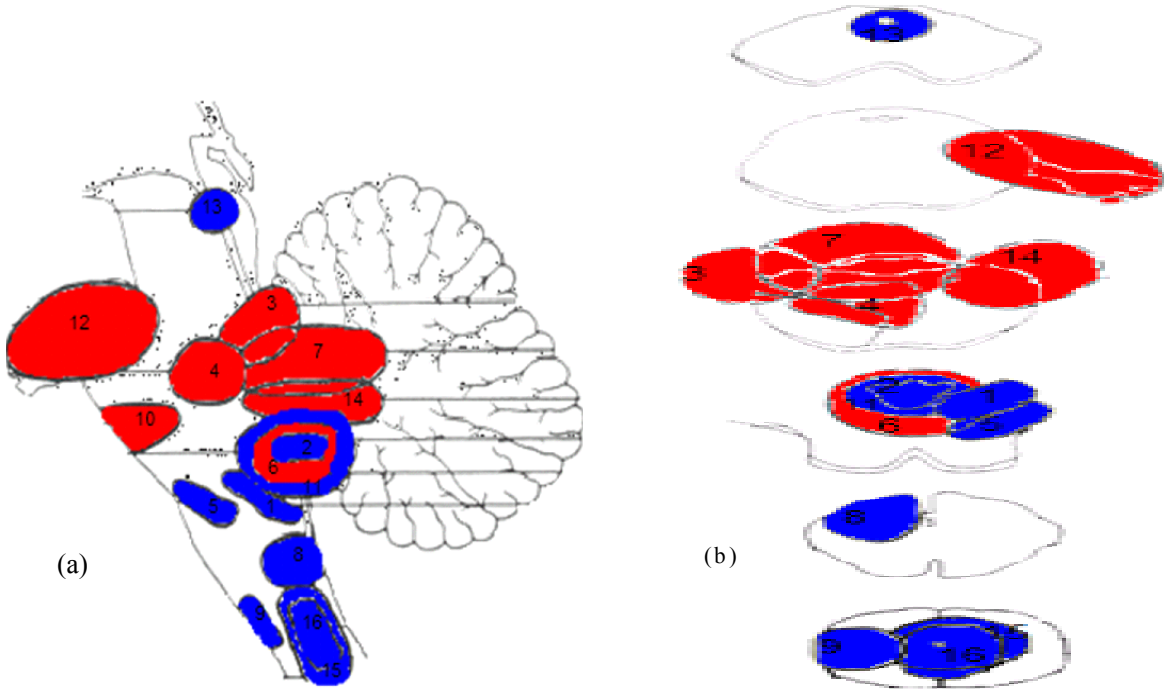
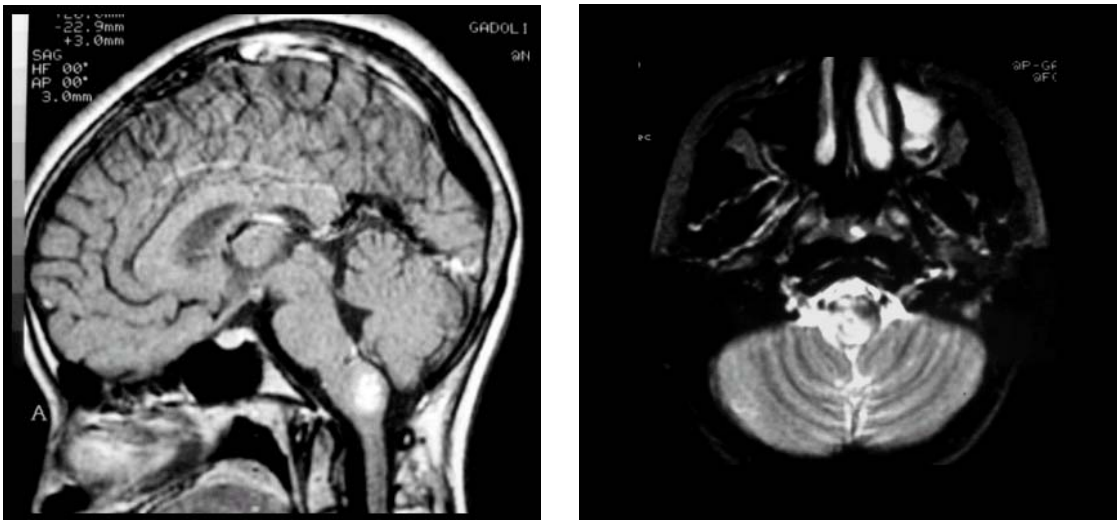


Fig. 1(a-b): Schematic representation of sites in which tumours locate in the brain-stem. Malignat tumours are located in the areas marked in red and the benign ones in areas marked in blue



(a) (b)

Fig. 2: (a): Sagittal T1-weighted showing a gadolinium-enhanced lesion in the medulla in the case 8 (low-grade astrocytoma). (b): T2-weighted MRI showing a focal mass in the medulla and which was a low-grade astrocytoma (case 8).

whereas the 7 that were operated on survive from 5 to 16 months. The cause of death was the recurrence of the tumor.

Brain-stem tumors encompass an array of heterogeneous lesions that may appear at any age. In our series we saw cases aged between 4 and 62 years. Gliomas are the most frequent tumoral lesions in the brain-stem with special tendency to present in chilhood[14,52,11,4]. Like in other studies, we did not see predilection by sex[14,52,11,4].

The mean duration of symptoms before diagnosis does matter greatly. Relationship between duration of sympton and prognosis has been previously encountered[51,49,11,35,33,12], with benign tumors having period of symptoms longer than 6 months before diagnosis[11]. Guillamo *et al*. concluded that in adults duration of symptoms longer than 3 months in brain stem gliomas is a good pronostic indicator[39]. In our series the duration of symptoms was shorter than 5 months in malignant tumors.

Due to the high concentration of axons in brain-stem structures the symptoms of tumors at this location can appear before these are detected by neuroradiologic techniques[21,51]. Our patients presented frequently with cranial nerve dysfunction, cerebellar symptoms and pyramidal-tract symptoms. These symptoms were also the most frequently found in other series[8,55,66]. In ten cases (30%) we observed symptoms of intracranial hypertension. Similar proportion (20%) had intracranial hypertension in the series of Badhe. We saw that malignant tumors located in the pons and had shorter symptom duration until diagnosis.

Brain-stem tumours account in one of every 5 cases of brain tumors in children and less frequently in adults with gliomas being the most common[5,11,12,33,51,59]. The broad spectrum of histopathology appeared in our series was also present in other studies[15,40,56,62,24,48]. The proportion malignant/benign tumors was 36.7/63.3% in our series and this proportion was similar to that found by, Tomita *et al*.[64]. Among malignant tumors the most frequent were high-grade astrocytomas as it was observed by other authors[33,50,51].

As it was expected MRI was superior to CT to detect brain-stem tumors. CT only detected 62.5% of the lesions in comparison to 100% detected by MRI. Given the high diagnostic accuracy of MRI in brain-stem gliomas, biopsy prior surgery is discouraged in many centres[43,13,31,67,38,5], especially in diffuse and infiltrative gliomas[5,18]. This does not mean that MRI is substitutive of histopathology[7,8]. Biopsy and/or surgery is especially recommended in tumors with well-defined borders, exophytic component[3,16,37] and those cystic and of cervicomedullary location because they are virtually benign[29].

On the basis of CT and MRI characteristics there are several modes of classifying brain-stem tumors to identify those amenable to surgery (44). The first systems were based on CT images in the 80s[23,63]. Once MRI emerged other systems of classification appeared in the 90s[2,10,17] with the aspect of the epicentre (focal or diffuse) being the main criterion. The more complex systems classify tumors by location, aspect focal or diffuse, presence/absence of hydrocephalus and growth pattern[44]. For classification purposes we use the following criteria: location, aspect of the tumor border (well defined or diffuse) and the presence/absence of exophytic component.

Albright and coworkers determined the prognostic importance of tumor location and that 100% of midbrain tumors had excellent prognosis[5]. Another report showed that tectal tumors are benign[38]. Cervicomedullary tumors are mostly low-grade tumors[24,45].

We found that pontine and pontine-medullary tumors are mostly malignant, (10/16) and especially those purely pontine. The bad prognosis of pontine tumors has been also found in other studies[5,11,47]. A survival of only 18% was achieved at 3-5 year follow-up[5].

The radiological tumoral border (aspect focal or diffuse) was important in our study. Most lesions (93.75%) with well-defined border were benign. In turn, lesions with diffuse borders were mostly malignant (71.4%). According to Albright *et al*. focal lesions had favorable outcome with 85% survival rate at 3-5 years[5]. Focal lesions are usually low-grade tumors[24,1,22,65,61]. However, some malignant lesions such as primitive neuroectodermal tumors may present like benign[11]. Diffuse lesions are associated with poor prognosis with a survival at most of 20% at 3-5 years[5].

Behnke regarded the pontine tumors with hypertrophyc aspect as malignant in general[11]. In childhood diffuse lesions are usually malignant[61]. Guillamo *et al*. found that in young adults (<40 years). In this series diffuse pontine-medullary tumors were low-grade gliomas, but in older patients these are mostly malignant[39].

In our series the exophytic component was equally represented in malignant and benign tumors. This component point to low-grade gliomas when appear in children[45]. There may be cases difficult to classify according to neuroimaging techniques and these may benefit from stereotactic biopsy. For example some tumors of diffuse aspect in neurofibromatosis may be benign and may benefit from surgery[54]. In addition biopsy could make it possible to evacuate cystic formations as it occurred in two of 4 cases with pontine lesions. However stereotactic biopsy of brain-stem carries serious risks. We saw tachiarritmia in two of 4 cases of pontine biopsy with spontaneous recovery. The use of intraoperative evoked potentials is mandatory. We observed dramatic improvement in conduction after decompression in two cases.

In our series 26 patients underwent surgery with total resection in 18 and partial in 8. In the series of

Pierre-Kahn *et al*. with 75 children operated from brain-stem tumors the proportion of partial resection was 44,5%, subtotal in 32% and total in 23,5%[57]. Postoperative morbidity should not surpass 20%[57]. In our series morbidity was 30% (9/26) with favorable outcome and this may be due to the higher proportion of total resection.

In conclusion, a broad array of tumors may appear in the brain-stem with gliomas being the most frequent ones. A prognosis can be established according to the location and radiological aspect. Benign tumors use to be focal and to locate in the midbrain, medulla and cervico-medullary junction. Conversely, malignant lesions are mostly diffuse in aspect and tend to locate in the pons. The location and aspect of brain-stem tumors are of help in the surgical approach of the patients.

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