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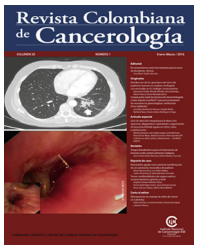

REVIEW ARTICLE

State of the art: pediatric brain stem gliomas☆

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KEYWORDS
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Abstract Brain stem gliomas are a heterogeneous group of tumors regarding both clinical presentation and prognosis. They can be classified on the basis of their biological behaviour, anatomical location and radiographic appearance on MRI. The choice of treatment depends largely on whether the tumor is a diffuse intrinsic pontine glioma or not. A better understanding of the biology of these tumors can be the key for progress in treatment. The purpose of this article is provide updated information to enable a detailed understanding of this group of tumors and thus help to optimize the management of this condition in the pediatric population.

PALABRAS CLAVE
Gliomas del tronco cerebral;
Niños;
Biopsia;
Resonancia magnética;
Terapia

Estado del arte: Gliomas del tronco encefálico en pediatría

Resumen Los gliomas del tronco encefálico son un grupo heterogéneo de tumores tanto en la presentación clínica como en el pronóstico. Se pueden clasificar en función de su comportamiento biológico, localización anatómica y la apariencia radiográfica en la RM. La elección del tratamiento depende en gran medida de si el tumor es un glioma intrínseco difuso del puente o no. Una mejor comprensión de la biología de estos tumores puede ser la clave para el progreso en el tratamiento. El propósito de este artículo es proporcionar información actualizada que permita una comprensión detallada de este grupo de tumores y así ayudar a optimizar el tratamiento de esta condición en la población pediátrica.

Abbreviations: DIPG, diffuse intrinsic pontine glioma; RT, radiotherapy; VP shunt, ventriculoperitoneal shunt; TMZ, temozolomide; PFS, progression-free survival; OS, overall survival.

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Introduction

The term ''brain stem gliomas'' is an inaccurate unifying classification- suggesting that these tumors share the same behaviour when in fact their biology is very heterogeneous, comprising low grade and high grade tumours, with significant differences in clinical picture, treatment and prognosis. Treatment and prognosis depends not only on the histological features, but also its location within the brain stem. In recent decades, the treatment has progressed significantly, a consequence of advances in imaging technology and microsurgical techniques. Surgery is the initial treatment of choice in the focal gliomas and chemotherapy is used only in persistent, recurrent or inoperable cases. Furthermore, the conformal external beam radiation therapy is the only known effective treatment for diffuse intrinsic pontine glioma (DIPG), but thanks to recognition by the scientific and medical community of the importance of biopsy in the past years, there has been an explosion in biological studies that keep opening the possibility of new treatments.[1] In this article, the most recent literature on brain stem gliomas, including epidemiology, pathology, classification, symptoms, diagnosis, treatment and prognosis is reviewed; with focus on possible future therapy and in order to help optimize the management of this condition in children and adolescents and be a support for future studies that let us improve the survival of patients with these tumors.

The authors conducted a search of references of recent articles addressing the subject of interest in the database MEDLINE, through PubMed search engine using keywords, combining various operators and search filters. Subsequently the selected articles were downloaded using the database of the university's library.

Epidemiology

Brain stem gliomas account for 10–20% of all primary CNS tumors in childhood and adolescence[1,2] accounting for ~200–300 cases per year in the US. It is one of the most difficult to treat in pediatrics.[3]

The average age of onset is from 5 to 10 years old and the ratio is 1:1 among boys and girls. There are no recognized premalignant lesions; however, a number of familial cancer syndromes have been associated with it, including neurofibromatosis type 1, Li-Fraumeni syndrome, and tuberous sclerosis, among others.[4]

Pathology

The latest WHO classification of CNS tumors maintains the grading system for tumors in general and is based on four histological criteria to determine the degree of malignancy: degree of nuclear pleomorphism, degree of mitosis, vascular proliferation and necrosis. The criteria for each type of tumour apply only to untreated tumors, because the therapy can alter tumor morphology.[5,6] Therefore, the WHO system recognizes four degrees of malignancy for astrocytic tumors, providing an estimate of their biological behavior and covers grade I astrocytomas, the least aggressive that can be cured by surgery alone, up to grade IV astrocytomas; highly aggressive tumors, infiltrating the surrounding brain tissue and fatal within an average of one year.[6] See Table 1.

Table 1 WHO Grades of CNS tumours.[5]

Astrocytic tumours	I	II	III	IV
Pilocytic astrocytoma	.			
Subependymal giant cell astrocytoma	.			
Pilomyxoid astrocytoma		.		
Diffuse astrocytoma		.		
Pleomorphic xanthoastrocytoma		.		
Anaplastic astrocytoma			.	
Glioblastoma				.
Giant cell glioblastoma				.
Gliosarcoma				.

Unfortunately, 85% of brain stem gliomas are high-grade gliomas and most of these correspond to diffuse intrinsic pontine glioma (DIPG).[7]

Diagnosis, clinical picture and images

Today, many authors believe that you can make a reliable diagnosis without a histopathological diagnosis. In fact, in 2007 Schumacher and colleagues carried out a blind review of the clinical, radiological and histological data of 142 pediatric cases with brain stem involvement, including 78 cases diagnosed with gliomas. The three observers were able to correctly identify lesions on magnetic resonance imaging (MRI) in 96.5% of cases on average; concluding that biopsy can be reserved for atypical cases.[8,9]

Other studies have evaluated the correlation between MRI characteristics and histopathological diagnosis of diffuse high-grade glioma in patients with intrinsic brainstem lesions, finding accuracy of diagnosis in 90% of enhancing lesions on MRI.[10] But in turn, in a series of 44 patients with suspected DIPG, 10% had a different histopathological diagnosis from glioma[11] and in a cohort of adults, the diagnosis was different from the original in 9 of 13 cases.[12] Additionally, in 2011, Hankinson et al. reported the results of a survey of pediatric neurosurgeons on MRI findings in selected cases of DIPG (including typical and atypical cases): 75% or greater agreement about whether a tumor was typical or atypical was found only in 43.8% of cases and it was concluded that in clinical practice, diagnosing DIPG based only on imaging characteristics and medical history, does not reach the appropriate threshold to be considered a standard management.[13]

However, the Second Consensus Conference of Pediatric Neurosurgery has endorsed the conclusion recorded by Schumacher[14] and therefore beginning treatment without pathological confirmation is an accepted practice. However, several authors emphasize the importance of an histopathological diagnosis and highlight that although many experimental agents have been tested in recent decades, there is currently no evidence of improved overall survival in this group of patients, and only detailed knowledge of these tumors can allow the development of new agents and improve results, a process that undoubtedly requires the availability of tumor tissue.[11]

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