Review Article

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Clinical Presentation, MRI findings and Molecular insights in Diffuse Intrinsic Pontine Gliomas (DIPGs): A Comprehensive Review

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Introduction: Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive and the most common brainstem tumor affecting pediatric patients, with a poor prognosis and limited treatment options. Despite extensive research, the median overall survival remains low, and current treatment mainly relies on radiotherapy. Recent discoveries of recurrent somatic mutations, particularly in histone 3 variants, have led to a reclassification of pediatric diffuse gliomas. However, the relationship between genetic alterations, imaging features, and prognosis is not yet fully understood.

Methods: This is a narrative review

Results and conclusion: This review provides an overview of DIPG, including its clinical presentation, typical imaging findings (with a focus on MRI techniques), diagnostic challenges, treatment modalities, and recent advancements in molecular understanding. DIPG presents with characteristic neurological symptoms and often manifests as an expansile intra-axial mass in the pons, usually exhibiting typical MRI findings. Diffusion-weighted imaging and magnetic resonance spectroscopy can provide additional insights. Pathologically, most DIPGs are pediatric type of diffuse high-grade gliomas, with specific histological features and occasional leptomeningeal spread. Radiotherapy remains the mainstay treatment. However, clinical trials with new agents are ongoing, trying to improve outcomes for DIPG patients.

Keywords: diffuse intrinsic pons glioma, DIPG, brain pediatric tumor, tumorH3K27M, midline diffuse glioma

INTRODUCTION

Diffuse intrinsic pontine glioma (DIPG) is a malignant and highly aggressive brainstem tumor that primarily affects pediatric patients, resulting in a dismal outcome. It accounts for 75% to 80% of all brainstem tumors in children (1) and has a poor prognosis, remaining one of the leading causes of brain tumor-related deaths in childhood. DIPGs are histologically high grade diffuse gliomas characterized by the diffuse infiltration of tumor cells within the pons. Its diagnosis heavily relies on a combination of a short clinical history (<6 months) and typical appearance on magnetic resonance imaging (MRI) since surgical intervention is not commonly performed (2). Despite extensive research efforts, the prognosis for DIPG has shown little improvement, with a overall survival (OS) whithout treatment of approximately 4 months and with treatment, specifically radiotherapy, the OS duration improves by several months (3). Radiotherapy has been the mainstay of treatment, with proven efficacy (although limited) providing transient symptomatic improvement and in prolonging progression-free survival (4). Currently, there are no proven chemotherapeutic agents that have demonstrated a significant impact on patient outcomes (5).

The recent discovery of recurrent somatic mutations, such as the lysine 27 to methionine substitution in histone 3 variants (H3.3 and H3.1), has been identified in approximately 80% of diffuse brainstem tumors (6), transforming our understanding of their biology. These mutations have prompted in 2021 the World Health Organization (WHO) (7) to reclassify pediatric diffuse high grade gliomas into a distinct entity known as "diffuse midline glioma, H3K27-altered". Although H3K27-altered is the predominant variant detected, additional distinct histone mutations have been discovered in cases of DIPG (8). However, the relationship between these genetic alterations, imaging features, and clinical prognosis remains incompletely understood. The term "DIPG" maintains its relevance as a clinical-radiologic diagnosis that encompasses pontine intrinsic diffuse tumors, with many, but not all of them, being H3K27-altered (9).

In this review article, we aim to provide an overview of DIPG, describe its clinical presentation, typical imaging

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findings with a focus on conventional and advanced MRI techniques, diagnostic challenges, treatment modalities, and recent advancements in molecular understanding.In this review article, we aim to provide an overview of DIPG, describe its clinical presentation, typical imaging findings with a focus on conventional and advanced MRI techniques, diagnostic challenges, treatment modalities, and recent advancements in molecular understanding.

MATERIALS AND METHODS

This is a narrative review presenting the latest updates, author impressions, expertise, and point of view about DIPG.

RESULTS AND DISCUSSION

Clinical presentation

DIPG can occur at different age groups but is most common in children, with a median age at diagnosis of 6 to 7 years (9). Children typically manifest neurological symptoms for less than 3 months, although some may present symptoms as early as a few days, and in rare cases, up to 16 months (10). Persistent symptoms lasting longer than six months should be analyzed with caution, prompting consideration of other potential diagnoses, including demyelinating disease, vascular disease, and other types of tumors such as pilocytic astrocytoma (10). More than 50% of patients with DIPG present with the classic triad of cranial nerve deficits, cerebellar signs, and long tract signs. Common cranial nerve deficits include facial asymmetry and diplopia, while typical cerebellar signs include ataxia, dysmetria, and dysarthria (11). Long tract signs are observed as hyperreflexia, upward Babinski sign, and decreased strength. The presence of abducens nerve (cranial nerve VI) palsy is highly indicative of DIPG and is often the initial sign (11). Raised intracranial pressure is uncommon, unless posterior exophytic enlargement of the tumor causes obstructive hydrocephalus (less than 10% of the cases) (12).

Imaging findings

The diagnosis of DIPG is usually based on the combination of a typical clinical history and MRI findings since surgical intervention and biopsies are not commonly performed due to the morbidity related to the location of these lesions (12). Brainstem tumors on MRI traditionally present as focal and well-defined (20%) or diffuse (80%) lesions (9) and can be separated into DIPG, posterior exophytic/cervicomedullary gliomas, and focal tectal gliomas (12,13) (figure 1), with the main characteristics described in table 1. MRI of DIPG provides valuable and characteristic findings, with a high accuracy rate in the initial diagnostic imaging work-up (>95%) (14). The tumor usually appears as an expansile intra-axial mass involving more than

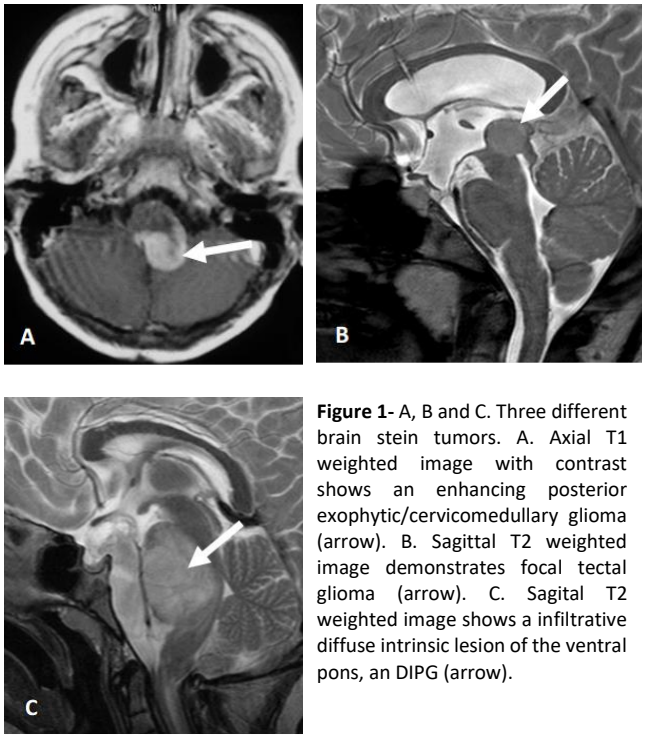


Figure 1- A, B and C. Three different brain stein tumors. A. Axial T1 weighted image with contrast shows an enhancing posterior exophytic/cervicomedullary glioma (arrow). B. Sagittal T2 weighted image demonstrates focal tectal glioma (arrow). C. Sagital T2 weighted image shows a infiltrative diffuse intrinsic lesion of the ventral pons, an DIPG (arrow).

Table 1 - Comparison of clinical and Neuroimaging Characteristics in Different Types of Brainstem Gliomas in children.

	Diffuse pontine glioma	Posterior exophytic/ Cervicomedullary glioma	Focal gliomas
Frequency	80%	15%	5%
Symptons	cranial nerve deficits, cerebellar signs, and long tract signs	Lower cranial deficits, motor/sensory deficits	Parinaud syndrome, hydrocephalus
Duration of symptons	<3 months	> 2 months	> 2 months
Location	Pons	Floor of the fourth ventricule or cervicomedullary	Tectal plate
Growth pattern	Infiltrative / prepontine extension	Exophytic or expansive	Focal, well defined
Imaging characteristics	Diffuse involviment of the pons/ ill-defined borders/ T2 hyperintensity	Exophytic growth/ well defined borders/ T2 hyperintensity	Focal lesion/ well defined borders/ T2 hyperintensity
Contrast enhancement	Variable/ heterogeneous enhancement	Usual enhancement	Variable/usual no enhancement
Diffusion weight imaging	Areas of restriction	Usual no restriction	Usual no restriction
Histology	Diffuse high-grade gliomas	Pilocytic astrocitoma and Diffuse low-grade glioma	Diffuse low-grade glioma

75% of the pons by cross-sectional area, primarily in the basis pons, and often shows ventral exophytic growth, with engulfment of the basilar artery (15)(figure 2). There is a possible extrapontine lesion extension in DIPG classified according to the direction, with horizontal extension toward the middle cerebellar peduncles (figure 3), which correlates with a shorter overall survival (OS), and vertical extension toward the hindbrain and/or medulla oblongata associated

with a longer OS (14). These tumors often demonstrate hypointensity on T1-weighted images and hyperintensity on T2-weighted images, usually heterogeneous, reflecting their infiltrative nature and edema (12,14) (figure 2). Contrast-enhanced MRI may reveal variable enhancement prevalence, up to 70% (9), with different patterns ranging from minimal enhancement to heterogeneous or ring-enhancement (figure 4). Some studies have reported a shorter OS in patients with enhancement (9), and Jansen and colleagues (16) demonstrated that ring enhancement of the tumor (figure was associated with a negative predictor of OS and incorporated into a survival prediction model. Conway and colleagues (15) described an MRI semiological sign, occult enhancement on T1 subtraction images in DIPG, as a marker for angiogenesis. Typical and atypical MRI presentations have been described. DIPG with typical neuroimaging presentation exhibits as an expansile lesion located in the ventral pons, occupying more than 75% of the cross-sectional area of the pons on at least one transverse T2-weighted image. Atypical DIPG presentation is characterized by a predominant pontine or pontobulbar location, eccentricity, disproportional extrapontine extension, <75% cross-sectional involvement, well-defined margins, too much or no enhancement at all in post-contrast T1-weighted images (17).

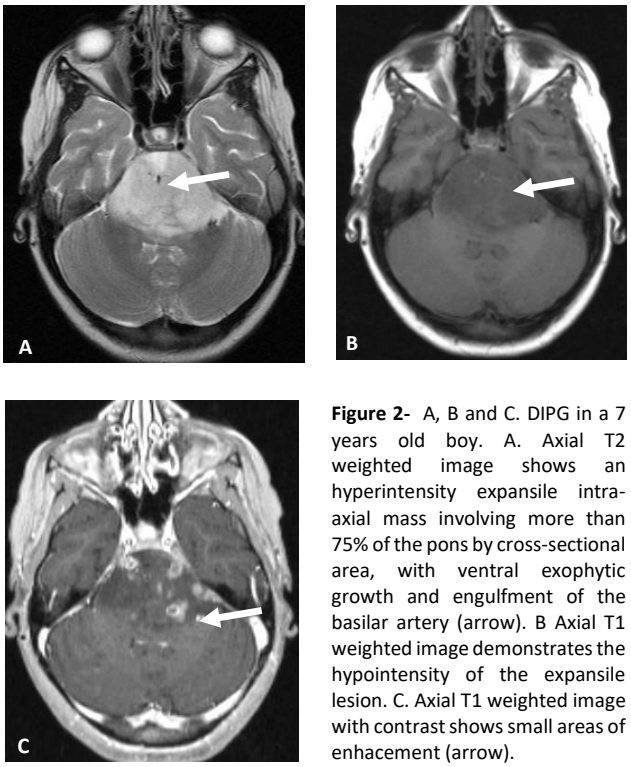


Figure 2- A, B and C. DIPG in a 7 years old boy. A. Axial T2 weighted image shows an hyperintensity expansile intra-axial mass involving more than 75% of the pons by cross-sectional area, with ventral exophytic growth and engulfment of the basilar artery (arrow). B Axial T1 weighted image demonstrates the hypointensity of the expansile lesion. C. Axial T1 weighted image with contrast shows small areas of enhacement (arrow).

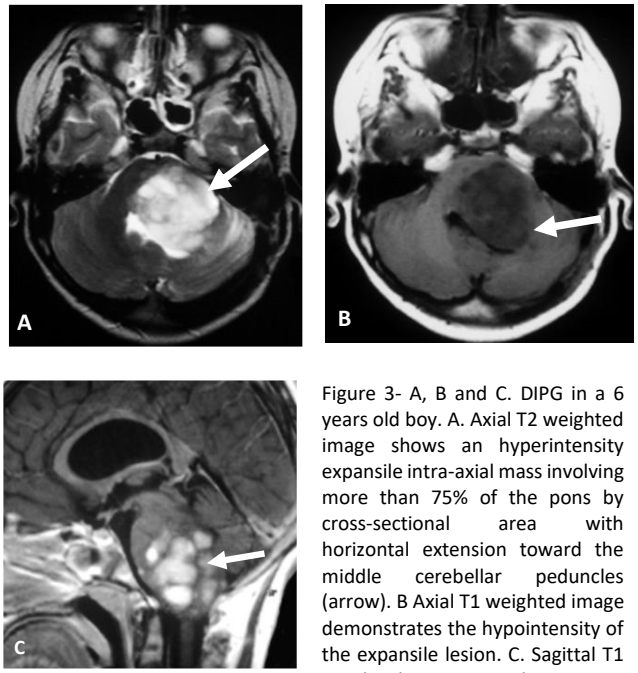


Figure 3- A, B and C. DIPG in a 6 years old boy. A. Axial T2 weighted image shows an hyperintensity expansile intra-axial mass involving more than 75% of the pons by cross-sectional area with horizontal extension toward the middle cerebellar peduncles (arrow). B Axial T1 weighted image demonstrates the hypointensity of the expansile lesion. C. Sagittal T1 weighted image with contrast shows large areas of enhacement with vertical extension toward the medulla oblongata (arrow).

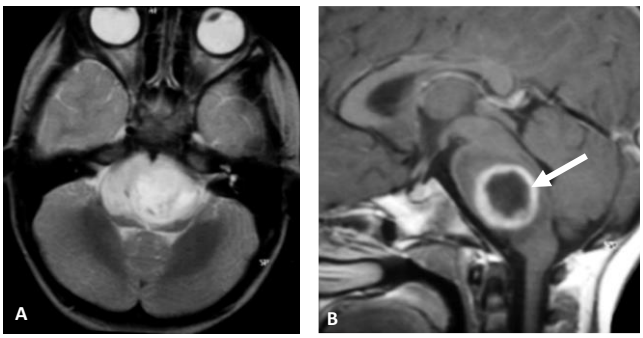


Figure 4- A and B. DIPG in a 6 years old girl. A. Axial T2 weighted image shows an hyperintensity expansile intra-axial mass involving more than 75% of the pons by cross-sectional area. B Sagittal T1 weighted with contrast image demonstrates a typical ring enhacement (arrow).

Tumor necrosis can be observed in 45% of the patients and presents as areas of well-defined, peripheral, or rim-like enhancement and typically fluid-like signal within the tumor. Hemorrhage is also reported, and the performance of SWI and GRE sequences increases sensitivity and is present in half of the patients (9). Diffusion-weighted imaging (DWI) can be used to assess the diffusion properties of the tumor. DIPG typically shows areas of restricted diffusion, characterized by hyperintensity on DWI and hypointensity on apparent diffusion coefficient (ADC) maps in most tumors (9). This restricted diffusion is attributed to the high cellularity and compact growth pattern of the tumor and can correlate with

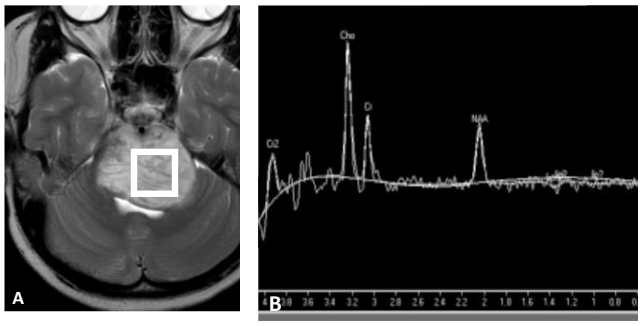
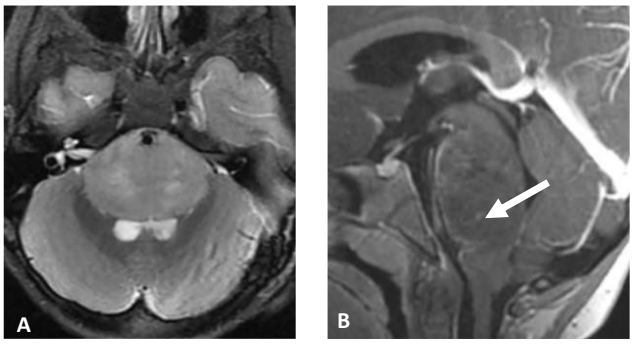


Figure 5- A and B. DIPG in a 7 years old girl. A. Axial T2 weighted image shows an hyperintensity expansile intra-axial mass involving more than 75% of the pons by cross-sectional area and the position of a single voxel box for magnetic resonance spectroscopy (MRS). B. MRS with 144 ms TE, demonstrates the typical elevated Choline (Cho) and reduced N-acetylaspartate (NAA).



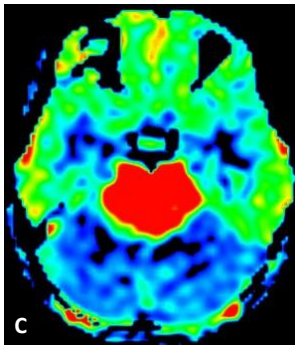


Figure 6- A, B and C. DIPG in a 6 years old boy. A. Axial T2 weighted image shows an hyperintensity expansile intra-axial mass involving more than 75% of the pons by cross-sectional area. B Sagittal T1 weighted image with demonstrates the enlargement of the ventral pons e minimal enhancement. C. Perfusion weighted image, dynamic susceptibility contrast-enhanced (DSC) imaging shows a high relative cerebral blood volume (arrow).

a shortened survival (18,19). Magnetic resonance spectroscopy (MRS) is an advanced imaging technique that measures concentrations of metabolites in tissues. Usually, in DIPG, MRS demonstrates elevated choline (figure 5), which is found in cell membranes and often elevated in tumors due to increased cell turnover. It also shows decreased N-acetylaspartate (NAA), a marker of neuronal integrity that tends to decrease in tumors. Additionally, it can demonstrate lactate peaks related to hypoxic conditions (12).

Another advanced imaging technique is magnetic resonance perfusion (Figure 6), which can provide noninvasive assessment of dynamic parameters and vascularity of the tumor. This technique can help differentiate between higher and lower grade tumors, as well as distinguish recurrent tumor from treatment changes, such as radiation necrosis (9). In DIPG, dynamic susceptibility contrast-enhanced (DSC) imaging shows that a higher baseline relative cerebral blood volume (rCBV) as well as an increase of rCBV during treatment is associated with reduced survival (20). Distant disease in DIPG has been infrequently studied, and the literature regarding baseline prevalence is limited. Spinal dissemination is rare but a strong predictor of poor OS (9). The differential diagnosis includes midbrain glioma, cervicomedullary glioma, cavernous malformation, demyelinating disease, infectious diseases including abscess, and metastasis.

Pathology and molecular findings

Due to the possible morbidity, most patients do not undergo biopsy or resection of their tumors, although some centers have incorporated stereotactic biopsy for pathological diagnosis (12). The histopathological analysis demonstrates different entities, although most DIPGs are diffuse high-grade gliomas, showing anaplasia, vascular proliferation, necrosis, and increased mitoses (12). Less common are diffuse low-grade gliomas, pilocytic astrocytoma, ganglioglioma, and embryonal tumors (17,21). In histopathological analysis, some DIPG patients presented with leptomeningeal spread. Extrapontine lesion extension with diffuse invasion of the brainstem, spinal cord, and thalamus was also observed in some patients, and even a distant spread to the frontal lobe was reported (21).

Recent genomic studies have revealed differences in pediatric and adult diffuse high-grade gliomas. Unique epigenetic reprogramming has been found in pediatric type diffuse high-grade gliomas (pHGG), characterized by recurrent mutations in genes encoding histone H3 variants, which are not found in other types of cancer. Supratentorial pediatric HGG exhibits mutations in H3F3A, encoding histone H3.3, with G34R/V observed in hemispheric tumors and K27M occurring in the midline. Most DIPGs present K27M mutations in genes encoding H3.3 (H3F3A) and H3.1 (HIST1H3B and HIST1H3C). These mutations, occurring in the N-terminal tail of H3 genes, characterized by a substitution of the lysine at position 27, are the driving events in DIPG oncogenesis, resulting in a global loss of H3K27 trimethylation (8).

The type of histone affected by K27 has a significant impact on patient survival. Tumors with H3.1 mutations exhibit a better treatment response, mainly to radiotherapy, a less aggressive clinical course, and a lower incidence of metastasis compared to H3.3 mutated tumors. It is also a better predictor for survival than the DIPG clinico-radiological risk score (8). Chiang and colleagues (17) have observed that, on conventional neuroimaging, H3 K27M-mutant tumors with typical MRI presentation are

epigenetically and clinically similar to H3 K27M-mutant tumors with atypical MRI presentation. In a recent study, Rameh and colleagues (22) demonstrated that MRI features, including ADC histogram metrics, show differences among the various H3K27 mutations and H3 wild-type DIPG.

Treatment

Due to their location in the pons and infiltrative nature, DIPGs are unresectable tumors. Conventionally fractionated radiotherapy remains the established treatment for children with DIPGs, but hypofractionated radiotherapy has demonstrated encouraging outcomes compared to conventional radiotherapy (12). Typically, radiotherapy is administered to the tumor at a total dose of 54 Gy over six weeks, with daily fractions of 1.8 Gy. However, hypofractionated radiation therapy utilizing fewer fractions, delivering a total dose of 39 Gy, has exhibited comparable results and improved tolerability, especially in young children. The combination of radiation with chemotherapy or immunotherapy may have synergistic effects in the treatment of DIPG (23).

Despite several clinical trials testing various therapies, none have demonstrated an increase in survival for children with DIPGs. However, these clinical trials have paved the way for future studies involving innovative agents that have shown efficacy in preclinical models (23).

DISCLOSURES

Ethical approval

Not appliable

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

The patient gave consent to use his information and images for publication.

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Contributions

- **Gustavo Novelino Simão**: Conceptualization, Supervision, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing

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