Diffuse Intrinsic Pontine Glioma

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Abstract

Diffuse intrinsic pontine glioma (DIPG) is a rare pediatric brain tumor that carries a very poor prognosis and lacks any effective treatment. Most seen in children, DIPG can also affect young adults. Presenting symptoms are often related to disruption of neural tracts traveling through the brainstem as patients present acutely with neuromuscular deficits, cranial nerve palsies, or signs of cerebellar involvement. Various epigenetic and genetic mutations have been documented, with mutations in the histone 3 protein family as well as the ACVR1 gene being heavily implicated. Diagnosis is typically made with the typical constellation of clinical presentation and imaging findings, although biopsy of the lesion may be utilized more in the future. While treatment centers around radiation therapy, it has not been shown to be drastically beneficial, and more research needs to be done to find more effective targeted and effective therapies.

Keywords: central nervous system, brain, neoplasm, malignant

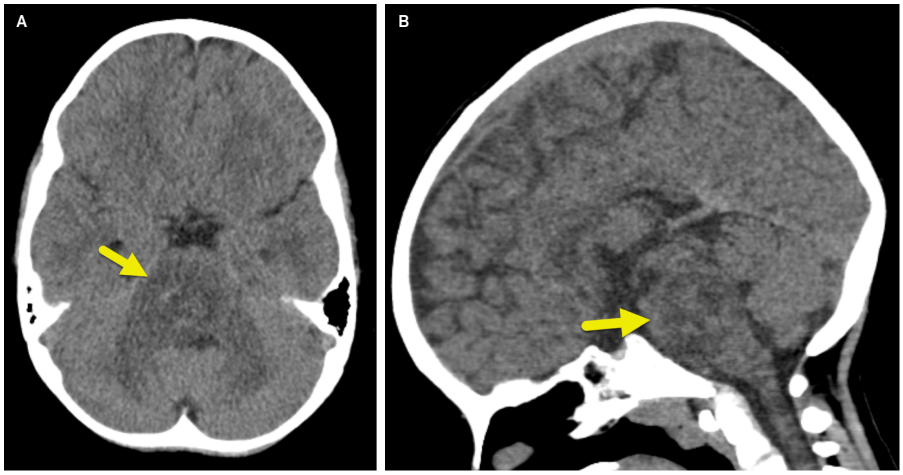
Case Summary

A toddler was brought to the emergency department following an episode of nonbloody nonbilious emesis and persistent drowsiness. He was found sleeping on the floor, raising concern for head injury. Neurological exam revealed a lethargic male with a fixed left gaze preference and an ataxic gait. Physical exam was otherwise unremarkable. Labs obtained included complete blood count (CBC), basic metabolic panel (BMP), and liver profile. Abnormalities on CBC were low white blood cell (3.68), hematocrit (33.8), absolute lymphocytes (1.59), and lymphocyte fraction (43.2). BMP and liver profile were unremarkable except for a low blood urea nitrogen (<5).

Imaging Findings

CT of the head (Figure 1) without contrast revealed a predominantly right-sided hypodense mass in the pons extending posteriorly and superiorly into the right middle cerebellar peduncle and inferiorly to the level of the pontomedullary junction. There was mild deformation of the ventral aspect of the 4th ventricle without obstructive hydrocephalus.

Figure 1. (A) Axial and (B) sagittal CT images of the head showing a hypodense mass (arrow) arising from the pons. The 4th ventricle is mildly deformed along the ventral aspect of the mass.



Subsequent MRI (Figure 2) showed a well-defined 3.2 × 3.7 × 3.2 cm pontine mass that was predominantly hypointense on T1 and hyperintense on T2 with moderate globular internal hemorrhage. Moderate peripheral diffusion restriction was also noted. In addition, an MRI of the spine was performed, which did not detect any abnormalities (drop metastases).

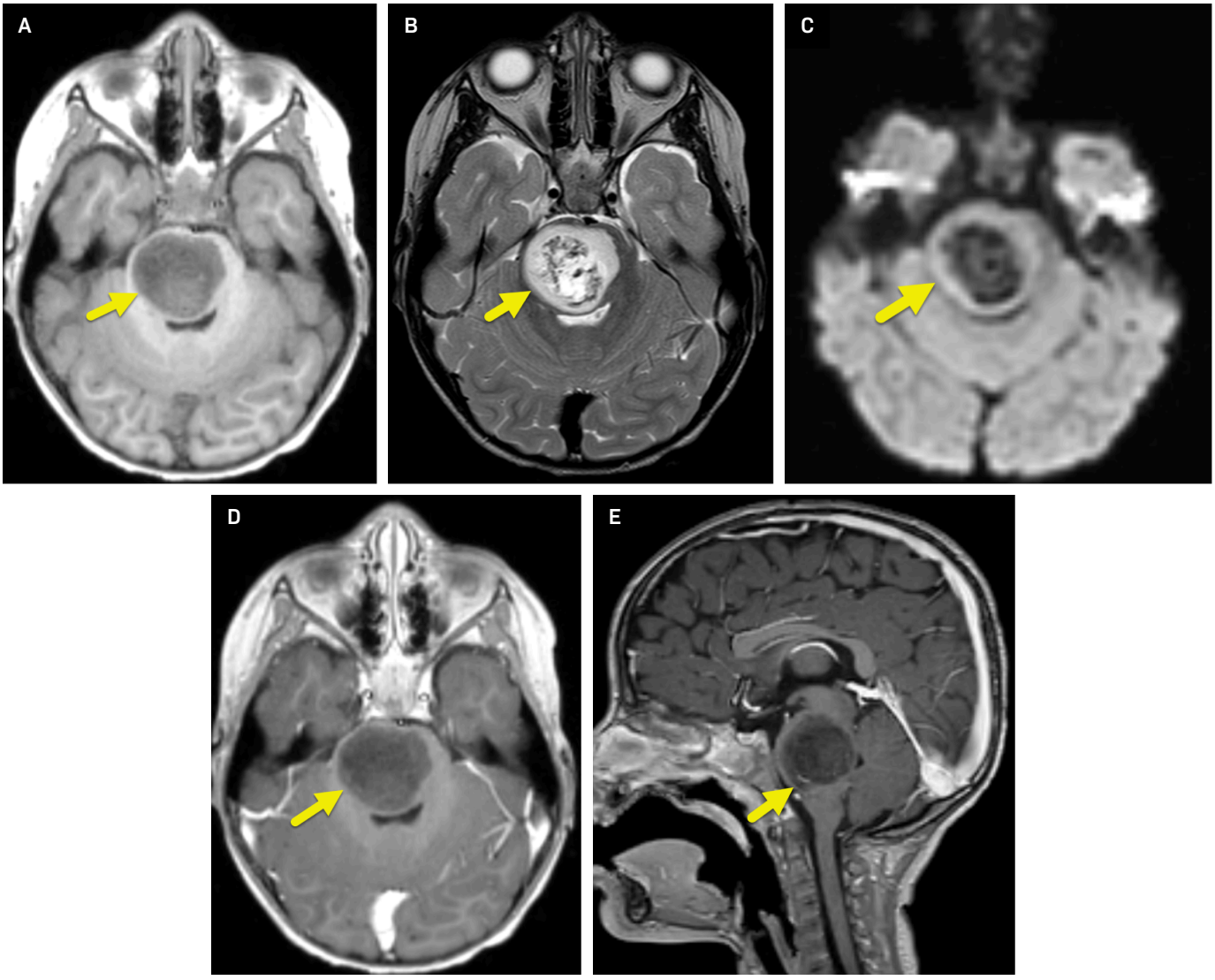
Diagnosis

Diffuse intrinsic pontine glioma (DIPG).

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Figure 2. (A) Axial T1-weighted, (B) T2-weighted, and (C) diffusion-weighted images showing the pontine mass (arrow). The mass is hypointense on T1-weighted images, heterogeneously hyperintense on T2-weighted images, and has mild peripheral restricted diffusion. The heterogeneous appearance on the T2-weighted images is due to mild internal hemorrhage. (D) Axial and (E) sagittal T1-weighted images obtained after the administration of contrast showing only minimal enhancement of the pontine mass (arrow).



Differential diagnosis of the brainstem lesion includes ependymoma, medulloblastoma, vascular malformations, encephalitis, hamartomas, demyelinating disorders, and Langerhans cell histiocytosis.

Discussion

DIPG is a rare brain tumor that is newly diagnosed in 100-150 children in the United States annually. It has a bimodal peak, affecting children with a median age of 6-7 years at diagnosis and adults with a median age of 34 at diagnosis. Outcomes remain poor, with a median survival time of 8-11 months and less than 10% of patients surviving 2 years after diagnosis.[1]

Patients with DIPG typically present acutely with any combination of long tract signs (eg, clonus, hyperreflexia, weakness), cranial nerve palsy (particularly of the 6th and 7th cranial nerves), and cerebellar signs. Tumor expansion may result in compression of the 4th ventricle, resulting in hydrocephalus.[1]

Histologically, most DIPGs are fibrillary astrocytomas, with higher grades demonstrating anaplasia, necrosis, and vascular proliferation.[2] Early genome sequencing found mutations in the histone H3 (H3K27M), TP53, and ACVR1 genes to be heavily implicated in DIPG tumorigenesis. Later research identified molecularly distinct subgroups within DIPG, each harboring their own complex set of mutations.[3,4] Extensive sequencing efforts have revealed the various intracellular signaling cascades that are disrupted in

DIPGs: cellular proliferation pathways (eg, receptor tyrosine kinase, MYC-N), cell cycle regulation pathways (eg, RB), or immune checkpoint pathways (eg, B7-H3 glycoprotein).[1]

Historically, DIPG was diagnosed based on symptoms and radiologic findings due to its precarious location. CT is often ordered shortly after presentation, as in our patient. CT usually demonstrates a hypointense pontine lesion with poorly delineated borders that, if exophytic, may encase the basilar artery and extend into the prepontine cistern.[4,5] MRI is the preferred imaging modality and often reveals a pontine lesion bound laterally by the middle cerebellar peduncles, cranially by the midbrain, and caudally by the medulla. These masses are iso- or hypointense on T1-weighted imaging and hyperintense on T2-weighted images. The tumor typically has minimal enhancement or no enhancement after contrast administration. Diffusion MRI has demonstrated the ability to differentiate between DIPG and demyelinating disease based on the associated mass effect and secondary displacement of white matter tracts by the tumor. Other advanced imaging techniques, such as MR spectroscopy, MR perfusion, and PET, have been used to evaluate DIPG.[5]

Long a controversial topic, biopsies of DIPGs were once viewed as risky procedures with little to no direct patient benefit and were reserved for select, atypical cases. Recent evidence has established that biopsies can be performed safely with acceptable morbidity.[1,6] Biopsies provide opportunities for personalized therapies, as the current treatment regimen is heavily reliant on radiation therapy and radiosensitizing, neoadjuvant, or adjuvant chemotherapy. The benefits of personalized therapy are controversial, with some studies citing a 3-6-month increase in survival while others claiming its benefits are mostly palliative.[1,5,7] Newer therapies utilizing monoclonal antibodies directed against both the epigenetic and genetic aberrations (eg, histone methylase/acetylase inhibitors, anti-EGFR, anti-VEGF) are being developed and studied.[1,7]

Prognostically, diagnosis before age 3 or over age 10 was associated with higher rates of long-term survival (LTS). Larger craniocaudal tumor dimension, extrapontine (exophytic) extension, tumor necrosis, and ring enhancement on imaging were associated with shorter survival. Finally, the K27M mutation in the histone 3.1 protein was associated with longer median survival and LTS compared with the same mutation in the histone 3.3 protein.[8]

Conclusion

DIPG is a rare pediatric brain tumor that carries a very poor prognosis and lacks any effective treatment. Most commonly seen in children, DIPG can also affect young adults. Presenting symptoms are often related to disruption of neural tracts traveling through the brainstem as patients present acutely with neuromuscular deficits, cranial nerve palsies, or signs of cerebellar involvement. Various epigenetic and genetic mutations have been documented, with mutations in the histone 3 protein family as well as the ACVR1 gene being heavily implicated. Diagnosis is typically made with the typical constellation of clinical presentation and imaging findings, although biopsy of the lesion may be utilized more in the future. While treatment centers around radiation therapy, it has not been shown to be drastically beneficial, and more research needs to be done to find more effective targeted and effective therapies.

References

1) Rashed WM, Maher E, Adel M, Saber O, Zaghloul MS. Pediatric diffuse intrinsic pontine glioma: where do we stand?. *Cancer Metastasis Rev*. 2019;38(4):759-770. doi:10.1007/s10555-019-09824-2

2) Khatua S, Moore KR, Vats TS, Kestle JRW. Diffuse intrinsic pontine glioma-current status and future strategies. *Childs Nerv Syst*. 2011;27(9):1391-1397. doi:10.1007/s00381-011-1468-z

3) Wu G, Diaz AK, Paugh BS, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. *Nat Genet*. 2014;46(5):444-450. doi:10.1038/ng.2938

4) Buczkowicz P, Hoeman C, Rakopoulos P, et al. Genomic analysis of diffuse intrinsic pontine gliomas identifies three molecular subgroups and recurrent activating ACVR1 mutations. *Nat Genet*. 2014;46(5):451-456. doi:10.1038/ng.2936

5) Tisnado J, Young R, Peck KK, Haque S. Conventional and advanced imaging of diffuse intrinsic pontine glioma. *J Child Neurol*. 2016;31(12):1386-1393. doi:10.1177/0883073816634855

6) Gupta N, Goumnerova LC, Manley P, et al. Prospective feasibility and safety assessment of surgical biopsy for patients with newly diagnosed diffuse intrinsic pontine glioma. *Neuro Oncol*. 2018;20(11):1547-1555. doi:10.1093/neuonc/noy070

7) Long W, Yi Y, Chen S, et al. Potential new therapies for pediatric diffuse intrinsic pontine glioma. *Front Pharmacol*. 2017;8:495. doi:10.3389/fphar.2017.00495

8) Hoffman LM, Veldhuijzen van Zanten SEM, Colditz N, et al. Clinical, radiologic, pathologic, and molecular characteristics of long-term survivors of diffuse intrinsic pontine glioma (DIPG): a collaborative report from the international and european society for pediatric oncology DIPG registries. *J Clin Oncol*. 2018;36(19):1963-1972. doi:10.1200/JCO.2017.75.9308