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# Pediatric brain tumors: a histologic and genetic update on commonly encountered entities

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As our understanding of pediatric brain neoplasia flourishes, so does the development of diagnostic, prognostic, and predictive biomarkers. The neuropathologist uniquely stands at the crossroads between pathology and molecular genetics, often overseeing the creation, development, implementation, delivery, and reporting of the newest bioassays. This review serves to highlight the key microscopic and genetic features of the most common pediatric brain tumors. For example, INI-1 immunohistochemistry has assisted in identifying several previously unrecognized cases of rhabdoid cell-poor atypical teratoid rhabdoid tumor (ATRT). The latest discovery involving the tandem duplication and fusion *BRAF-KIAA1549* on chromosome 7q34 in pilocytic astrocytoma has drawn attention to the MAPK-ERK pathway and its potential chemotherapeutic manipulation. The newly identified *IDH1* mutation, which appears characteristic of "secondary astrocytomas," has yet to be studied in the pediatric population, but some researchers have extolled concomitant *BRAF-KIAA1549/IDH1* analysis in the neuropathologic workup of many astrocytomas. Through these and other advances, our understanding of pediatric brain tumors will continue to expand exponentially, and as such will set the stage for truly effectual future treatments.


## Introduction

Brain tumors are the most common form of solid neoplasia in children and, overall, are only second to leukemia in terms of frequency.[1] The most recent CBTRUS (Central Brain Tumor Registry of the United States) data revealed a brain tumor incidence of 4.74/100,000 person years, and a prevalence of 9.5/100,000 in children.[2] Pilocytic astrocytomas are by far the most frequent single entity (Table 1). Other common pediatric central nervous system (CNS) tumors include diffusely infiltrating astrocytomas, medulloblastoma, and ependymoma.

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The current classification and grading scheme for pediatric brain tumors was published by the World Health Organization (WHO) in 2007.[3] In addition to this accomplishment, significant advances continue to be made in the realm of molecular biology. Despite these positive steps, several pediatric brain tumors remain difficult to classify and hence manage clinically. What follows here is a summary of the most common pediatric brain tumors, highlighting their histology and the latest molecular genetic findings thereof.

## Gliomas

### Pilocytic astrocytoma, WHO grade I

Pilocytic astrocytomas (PAs) are well-circumscribed, slow-growing astrocytomas that are associated with a fa-

**Table 1** Relative frequencies of pediatric brain tumors[1]

| Tumor type | WHO grade | Percentage |
|---|---|---|
| Pilocytic astrocytoma | I, III* | 23.5 |
| Diffuse astrocytoma | II | 5 |
| Anaplastic astrocytoma | III | 7.2 |
| Glioblastoma (GBM) | IV | 7.2 |
| Pleomorphic xanthoastrocytoma | II-III* | 1.9 |
| Subependymal giant cell astrocytoma | I | 2.5 |
| Medulloblastoma | IV | 16.3 |
| Ependymoma | II-III* | 10.1 |
| Craniopharyngioma | I | 5.6 |
| Germ cell tumors† | N/A | 2.5 |
| Ganglioglioma | I-III* | 2.5 |
| Meningioma | I-III* | 2.5 |
| Supratentorial primitive neuroectodermal tumor | IV | 1.9 |
| Pineal parenchymal tumors‡ | II-IV | 1.9 |
| Atypical teratoid rhabdoid tumor | IV | 1.3 |
| Choroid plexus tumors§ | I-III | 0.9 |
| Desmoplastic infantile ganglioglioma/astrocytoma | I | 0.6 |
| Dysembryoplastic neuroepithelial tumor | I | 0.6 |
| Pituitary adenoma | N/A | 0.9 |
| Schwannoma | I | 1.3 |
| Neurofibroma | I | 0.3 |

*Grade III versions of these tumors are deemed "anaplastic."

†Includes germinoma, mature/immature teratoma, choriocarcinoma, embryonal carcinoma, yolk-sac tumor.

‡Includes pineocytoma, pineal parenchymal tumor of intermediate differentiation, pineoblastoma, papillary tumor of the pineal region.

§Includes choroid plexus papilloma (CPP), atypical CPP, chordoid plexus carcinoma (CPC).

vorable prognosis. The posterior fossa is the preferred pediatric site. Brainstem examples are often exophytic and arise from the dorsal aspect of the midbrain or medulla. Supratentorial sites of predilection include the optic pathway/hypothalamus (often associated with NF1) and the basal ganglia/thalamus. The classic radiologic appearance is of a cystic lesion with an enhancing mural nodule (Figure 1A, B).

Although generally considered solid, virtually every case of PA demonstrates at least a small amount of histologic infiltration into the adjacent native brain parenchyma. PAs are classically described as biphasic with: (1) Rosenthal fiber-rich compact areas containing bipolar or "piloid" cells, and (2) loosely textured microcystic areas that bear eosinophilic granular bodies and small cells with round–oval nuclei that are associated with short cytoplasmic processes (Figure 2A-C) . Immunohistochemistry for glial fribrillary acidic protein (GFAP) reveals dense positivity (Figure 2D). Degenerative atypia (typified by enlarged, pleomorphic, and hyperchromatic nuclei) and vascular hyalinization are both common. "Pennies on a plate" denote large cells with multiple peripherally located nuclei.

Several histologic features, taken out of context, may raise suspicion of a higher grade astrocytoma. Architecturally, foci of a PA may closely resemble diffusely infiltrating forms of astrocytoma. Microvascular proliferation (MVP), often "glomeruloid" in morphology, can closely mimic that found in high-grade gliomas and may take on garland-like (ie, linear) arrangements (Figure 2E). Bland "infarct-like" necrosis is frequent, but mitoses are usually sparse. Extension into the local subarachnoid space is fairly common, but it only rarely adversely impacts prognosis[4] (Figure 2F). Despite these pitfalls, rare anaplastic PAs, are acknowledged to exist. In a recent study of 2200 PAs, 34 (1.7%) of cases demonstrated anaplasia as typified by brisk mitoses

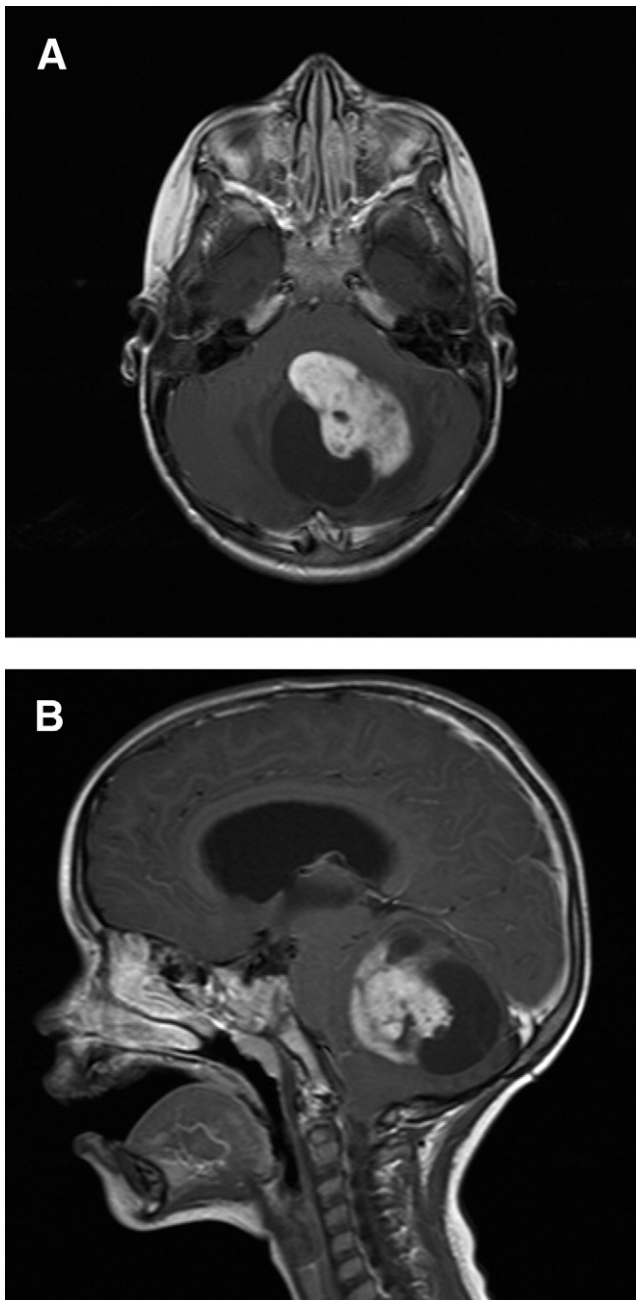


**Figure 1** Cerebellar PA. T1 MRI with gadolinium. (A) Axial. (B) Sagittal. Note the classic cystic appearance and the solid enhancing component (courtesy of the Radiology Department BCCH).