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REVIEW ARTICLE

The New World Health Organization Classification of Central Nervous System Tumors: What Can the Neuroradiologist Really Say?

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SUMMARY: The *WHO Classification of Tumors of the Central Nervous System* has become the worldwide standard for classifying and grading brain neoplasms. The most recent edition (*WHO 2007*) introduced a number of significant changes that include both additions and redefinitions or clarifications of existing entities. Eight new neoplasms and 4 new variants were introduced. This article reviews these entities, summarizing both their histology and imaging appearance. Now with more than 3 years of clinical experience following publication of the newest revision, we also ask, "What can the neuroradiologist really say?" Are there imaging findings that could suggest the preoperative diagnosis of a new tumor entity or variant?

ABBREVIATIONS: aCPP = atypical choriod plexus papilloma; CNS = central nervous system; CPP = choriod plexus papilloma; CPCa = choriod plexus carcinoma; DNET = dysembryoplastic neuroepithelial tumor; EVNCT = extraventricular neurocytoma; MB = medulloblastoma; MBEN = medulloblastoma with extensive nodularity; PA = pilocytic astrocytoma; PGNT = papillary glioneuronal tumor; PMA = pilomyxoid astrocytoma; PPTID = pineal parenchymal tumor of intermediate differentiation; PTPR= papillary tumor of the pineal region; RGNT = rosette-forming glioneuronal tumor; SCO = spindle cell oncocytoma; T1C+ = post-contrast T1-weighted; T1WI = T1-weighted imaging; T2WI = T2-weighted imaging; WHO = World Health Organization

The *WHO Classification of Tumors of the Central Nervous System*, now in its fourth edition, is the universal standard for classifying and grading brain neoplasms.[1,2] The most recent edition (*WHO 2007*) introduced a number of significant changes that include both additions and redefinitions or clarifications of existing entities. Eight new neoplasms and 4 new variants were introduced.[3] We review these entities, summarizing both their histology and imaging appearance. Now with more than 3 years of clinical experience following publication of the newest revision, we also ask, "What can the neuroradiologist really say?" Are there imaging findings that should suggest the preoperative diagnosis of a new tumor or variant?

What Is New with Gliomas?

Three new tumor types were added to the glioma section of *WHO 2007*. The first of these, angiocentric glioma, was recognized and codified as a distinct entity. The second, PMA, is now formally considered as a distinct more aggressive variant of PA. The third, a new type of choroid plexus tumor, aCPP, was recognized. Finally—although not a new entity—the terminology, histology, and etiology of pituicytoma was clarified in the fourth edition. The WHO groups pituicytoma with "tumors of the sellar region," not gliomas, so it is discussed in a subsequent section.

Angiocentric Glioma. Angiocentric glioma was assigned to the same histologic category (ie, "other neuroepithelial tumors") as chordoid glioma and astroblastoma.[4] Angiocentric gliomas are slowly growing solid hemispheric tumors of children and young adults. They are strongly epileptogenic, with >95% of patients presenting with intractable seizures. These tumors are characterized histologically by elongated bipolar glial tumor cells and by their striking perivascular growth pattern. Angiocentric gliomas have a low proliferative potential (MIB-1 between 1%–5%) and have been designated as WHO grade I neoplasms.

Only a few cases of angiocentric glioma with imaging findings have been reported.[5,6] The most commonly reported location is the frontal lobe. Angiocentric gliomas are typically well-delineated cortically based lesions that expand affected gyri and sometimes exhibit deep "stalk-like" extension toward the ventricle. A rim of subtle T1 shortening may surround the lesion, which is generally hypointense on T1WI and hyperintense on T2WI. Enhancement is typically absent (Fig 1).

So what can the neuroradiologist really say about angiocentric glioma? The major differential diagnosis includes DNET, oligodendroglioma, and ganglioglioma. While there are too few reported cases to describe definitive findings, think angiocentric glioma if a young patient with epilepsy has a cortically based tumor—especially in the frontal lobe—that exhibits T1 hyperintense rims or deep extension toward the ventricle. While angiocentric gliomas may appear somewhat cystic, DNETs have a more pronounced "bubbly" appearance. Oligodendrogliomas also tend to arise in the frontal lobes but occur in a somewhat older age group than angiocentric gliomas, often calcify, and typically originate at the gray-white matter interface. Gangliogliomas often enhance while angiocentric gliomas do not.

PMA. PMA differs from PA both clinically and histopathologically. PMAs typically occur at an earlier mean age and are associated with more aggressive behavior (and hence significantly worse prognosis) than PAs. PMAs are composed of bi-

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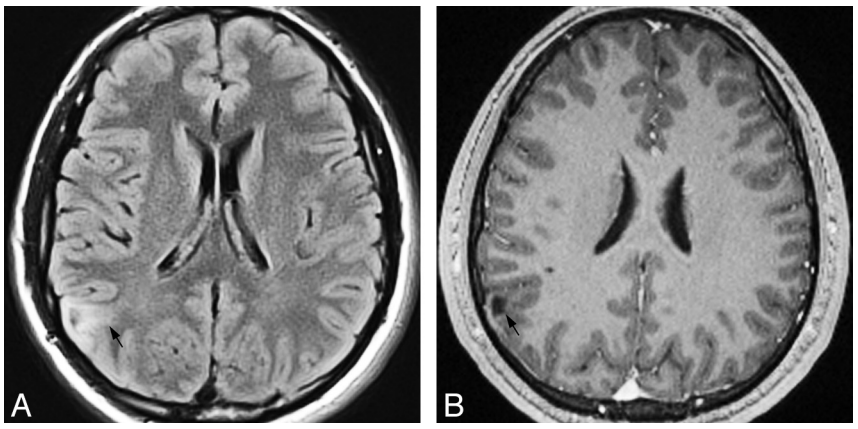

Fig 1. A young adult with intractable seizures. *A*, Axial fluid-attenuated inversion recovery image shows a hyperintense cortically based mass with subcortical stalk-like extension toward the ventricle (*arrow*). *B*, Axial T1C+ image shows an expanded gyrus with a hyperintense rim and hypointense center (*arrow*). Note subtle erosion of the inner calvaria. Angiocentric glioma was found at histologic examination.

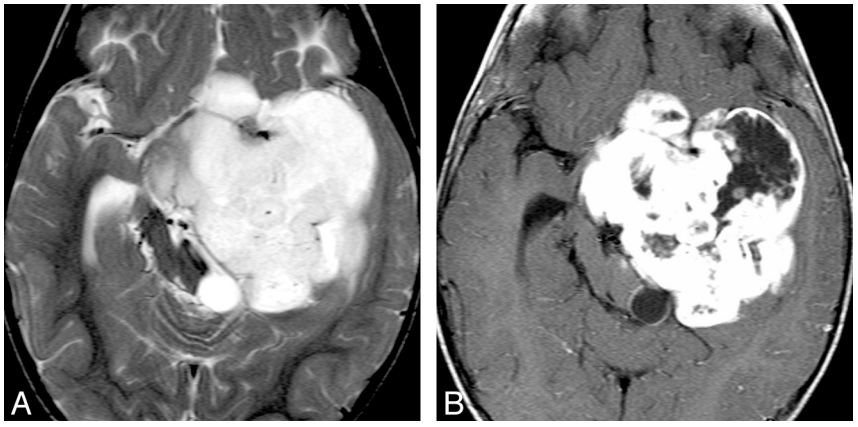

Fig 2. A 20-month-old child with failure to thrive. *A*, Axial T2WI shows a massive inhomogeneously hyperintense suprasellar mass with extension into the left temporal lobe. *B*, Axial T1C+ image shows strong but heterogeneous enhancement. Pilomyxoid variant of pilocytic astrocytoma was documented at surgery. Case courtesy of R. Hewlett, MD.

polar (piloid or hairlike) cells that lie within a distinct myxoid background matrix. PMAs are currently considered WHO grade II neoplasms (unlike PAs, which are grade I). Most recently, an "intermediate" pilomyxoid tumor that exhibits histologic features of both PMA and PA has also been described.[7]

Although they can be found virtually anywhere in the brain, the classic location of PMAs is the hypothalamus/chiasmatic region. A large bulky U-shaped suprasellar tumor that extends toward or into the adjacent temporal lobes is the most common appearance. Hemorrhage—rare in PAs—is found in 25% of PMAs, and >90% enhance after contrast administration. Approximately one-half of all PMAs demonstrate solid enhancement, but rim or heterogeneous enhancement is also common (Fig 2).[8]

So what can the neuroradiologist really say about PMA? The diagnosis should certainly be considered in an infant or young child with a bulky strongly enhancing suprasellar mass that contains hemorrhagic foci. We have found it useful to ask our neuropathologists to consider a diagnosis of PMA and to look for its specific histologic features in the biopsy specimen. In addition, including PMA in the differential diagnosis alerts the neuro-oncologist that the potentially worse prognosis associated with PMA may warrant more aggressive therapy.

aCPP. aCPP was recognized as a tumor intermediate in histology and graded between CPP (a WHO grade I neoplasm) and CPCa (a WHO grade III). Cellular atypia and increased mitotic activity are reflected in more aggressive biologic behavior, with earlier metastases and higher recurrence rates than CPP. An aCPP is designated as a WHO grade II neoplasm.[9]

Only a few imaging cases of aCPP have been reported in the literature.[10] All have the lobulated papillary appearance and strong uniform enhancement that also characterizes CPP. While both CPPs and aCPPs can usually be distinguished from CPCa's by the presence of parenchymal invasion in the latter, imaging findings do not distinguish CPP and aCPP, so this diagnosis remains a histologic one (Fig 3).

So what can the neuroradiologist really say? Simply on the basis of statistics, a lobulated, intensely enhancing intraventricular mass in a child younger than 5 years of age is most likely a CPP, not an aCPP or CPCa. Definitive tumor grade (I versus II) must await pathology. Because all choroid plexus neoplasms—regardless of grade—may metastasize to the CSF, the entire neuraxis should be imaged before any surgical intervention.

Neuronal and Mixed Neuronal-Glial Tumors

The most significant changes in this category of CNS neoplasms occurred in earlier versions with the recognition of DNET and central neurocytoma as distinct tumor entities.

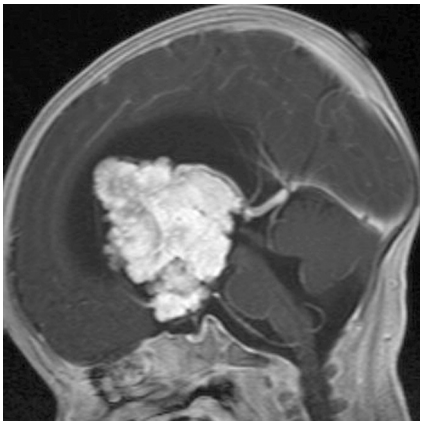

Fig 3. Sagittal T1C+ image in an infant with hydrocephalus shows an intensely enhancing lobulated mass in the third and lateral ventricles. Histologic diagnosis was aCPP (WHO grade II).

The 2007 version recognized 2 new tumors—PGNT and RGNT of the fourth ventricle—and 1 new variant, an extraventricular form of neurocytoma.

PGNT. Initially considered a ganglioglioma variant (*WHO 2000*), PGNT was recognized in 2007 as a distinct tumor entity.[11] It is a rare relatively well-circumscribed clinically indolent tumor that is exclusively found (so far) in the cerebral hemispheres. Patient age varies widely. PGNTs are biphasic tumors, with both astrocytic and neuronal elements. The histologic hallmark of PGNT is the presence of hyalinized vascular pseudopapillae.

Although PGNT was not formally assigned a WHO grade in the 2007 revision, this tumor generally behaves in a benign grade I fashion. Gross total surgical resection is the primary treatment. Recurrence or tumor progression is unusual.

Only a handful of PGNTs with imaging findings have been reported.[12] A mixed cystic-solid or cystic lesion with a mural nodule is the commonly reported appearance. The solid component typically enhances. No grossly apparent lobulated configuration is seen on imaging studies (Fig 4).

So what can the neuroradiologist really say about PGNT? We are most likely to diagnose a PGNT preoperatively as a ganglioglioma—and with good reason. The 2 tumors have virtually identical imaging appearance, and gangliogliomas are much more common (by far) than PGNTs. PGNT remains a histologic diagnosis.

RGNT. RGNT was first described in 2002 and then was codified as a new tumor entity in 2007. RGNTs are rare slow-growing tumors of young and middle-aged adults. The most common—but by no means the only—site is the fourth ventricle. RGNTs contain both neurocytic and astrocytic elements. Their histologic hallmark is the formation of neurocytic perivascular pseudorosettes. RGNTs are designated as WHO grade I neoplasms.

A classic RGNT is a heterogeneous-appearing mass centered within the fourth ventricle. The tumor often has a multicystic appearance. Hemorrhage and calcification are common, and enhancement is usually inhomogeneous (Fig 5).[11,13]

So what can the neuroradiologist really say? Primary fourth ventricular neoplasms in adults are relatively uncommon. While ependymomas and medulloblastomas are occasionally found outside the pediatric age group, ependymomas typically extrude through the lateral recesses and medulloblastomas rarely calcify. CPPs enhance intensely and uniformly. Therefore, if a fourth ventricular tumor is identified in an adult, RGNT should be included in the differential diagnosis. It has a better prognosis than either cellular ependymoma or medulloblastoma. Gross total resection may be curative without adjuvant therapy because CSF dissemination has not been reported to date, to our knowledge.

RGNTs have been reported in other sites such as the pineal gland and tectum, but their identification has only been made at histologic examination.

EVNCT. The term "central neurocytoma" describes a neuronal tumor with preferential location in the lateral ventricle body. These tumors comprise fibrillary areas mimicking neuropil plus collections of uniform round cells that have immunohistochemical and ultrastructural evidence of neuronal differentiation. A low proliferation rate is typical. Similar neoplasms have been reported outside the ventricular system, and the *WHO 2007* designated the term "EVNCT" for these uncommon tumors. Because the only distinguishing feature is location—not histology—EVNCTs are included in the same histopathologic code as central neurocytoma. Both central and extraventricular neurocytomas are designated as WHO grade II neoplasms.[14]

Few EVNCTs have been reported in the imaging literature.[15] Like their intraventricular counterparts, EVNCTs are generally tumors of young adults (median age is 34 years). The most common presenting symptom is epilepsy. EVNCTs are usually well-circumscribed mixed cystic and solid masses that demonstrate only mild vasogenic edema. They are heterogeneously hyperintense on T2WI. Calcification and hemorrhage may be present. Variable enhancement of the solid portion is typical (Fig 6).

So what can the neuroradiologist really say? While the location and bubbly appearance of a central neurocytoma are highly suggestive of this diagnosis, there are, to date, no distinguishing features that would suggest the preoperative diagnosis of EVNCT. A parenchymal mass in a young adult with epilepsy has a broad differential diagnosis. If the appearance is that of a cyst with a mural nodule, it is more likely to be a ganglioglioma. A nonenhancing bubbly-appearing cortical mass is much more likely to be a DNET (both WHO grade I neoplasms) than an EVNCT. Gross total resection of all these cortically based epileptogenic neoplasms is usually curative. The definitive diagnosis of EVNCT remains not an imaging but a histologic diagnosis.

Pineal Region Tumors

Two new tumors of the pineal region were codified in the *WHO 2007* classification, PTPR and PPTID.

PTPR. PTPR is a rare neuroepithelial tumor that arises from the subcommissural organ and exhibits ependymal differentiation. The mean age at diagnosis is 32 years. Macroscopically, PTPRs are indistinguishable from pineocytomas. Microscopically, the tumors are easily distinguished. PTPRs show papillary architecture with pseudostratified columnar epithelium. Ultrastructural features suggesting ependymal differentiation are present. Immunohistochemistry is positive for cytokeratins. While grading of PTPRs has yet to be defined,

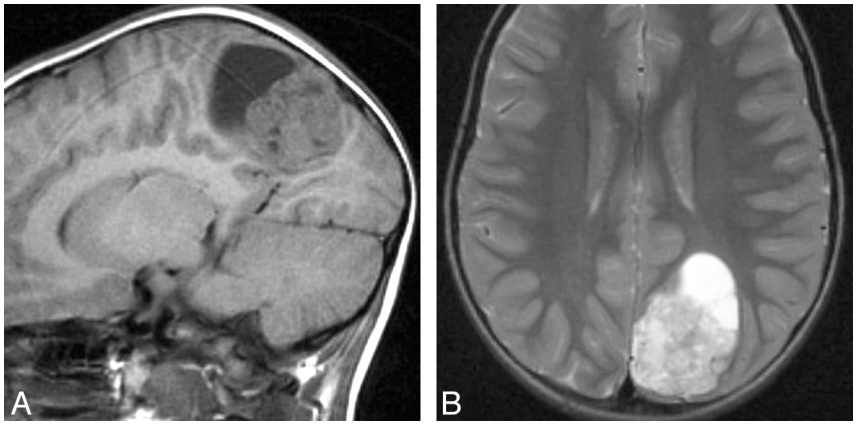

Fig 4. A child with long-standing seizures. *A,* Sagittal T1WI shows a mixed cystic-solid mass. *B,* Axial T2WI shows that the nodule is inhomogeneously hyperintense. No enhancement was seen on contrast-enhanced images (not shown). Histologic diagnosis was PGNT.

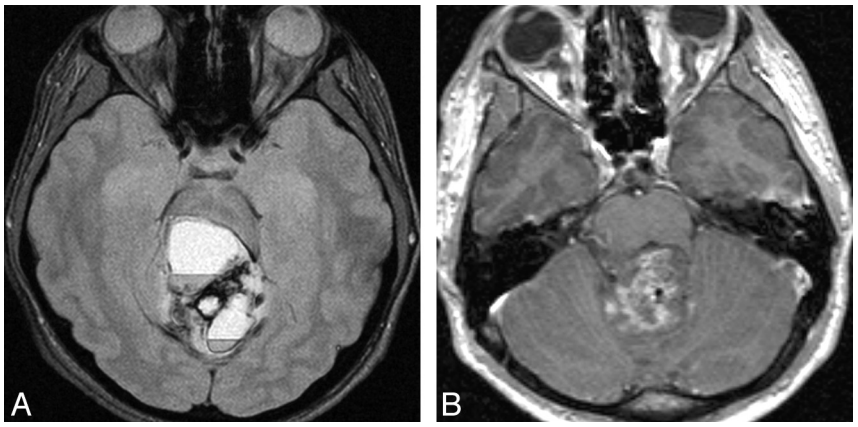

Fig 5. A 21-year-old man with headaches. *A,* Axial T2* image shows a mixed cystic-solid fourth ventricular mass with fluid-fluid levels and hemorrhage. *B,* Postcontrast axial T1WI shows inhomogeneous enhancement. Histology proved RGNT of the fourth ventricle.

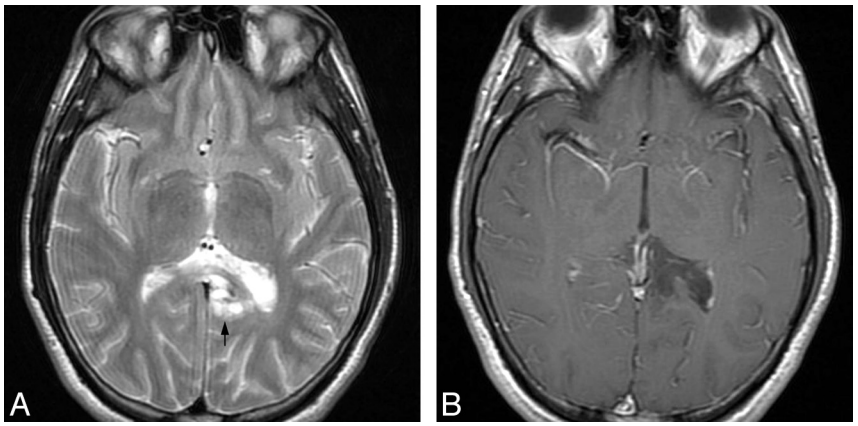

Fig 6. A 24-year-old man presented with seizures. *A,* Axial T2WI shows a bubbly-appearing mass in the left parahippocampal gyrus (*arrow*). *B,* T1C+ image shows no enhancement. Histologic examination disclosed extraventricular neurocytoma. Case courtesy of C. Glastonbury, MBBS.

most neuropathologists consider these as WHO grade II or III neoplasms.[16,17]

Only a few cases of PTPR with imaging findings have been reported in the literature.[18-20] These tumors tend to be large (2.5–4 cm), well-circumscribed, and partially cystic. T1 hyperintensity has also been described as a characteristic imaging feature.[18] Strong but heterogeneous enhancement is present (Fig 7).

So what can the neuroradiologist really say? PTPRs do not look like pineocytomas, and the typical patient age is too old for pineoblastoma. Therefore, a large heterogeneous enhancing pineal tumor in a middle-aged adult is most likely 1 of 3 rare diagnoses: PTPR, PPTID, or metastasis to the pineal gland from an extracranial primary neoplasm.

PPTID. PPTID is a newly recognized tumor intermediate in malignancy between pineocytoma and pineoblastoma. PPTIDs occur at all ages but are most common in middle-aged and older patients. Mild-to-moderate nuclear atypia and low-

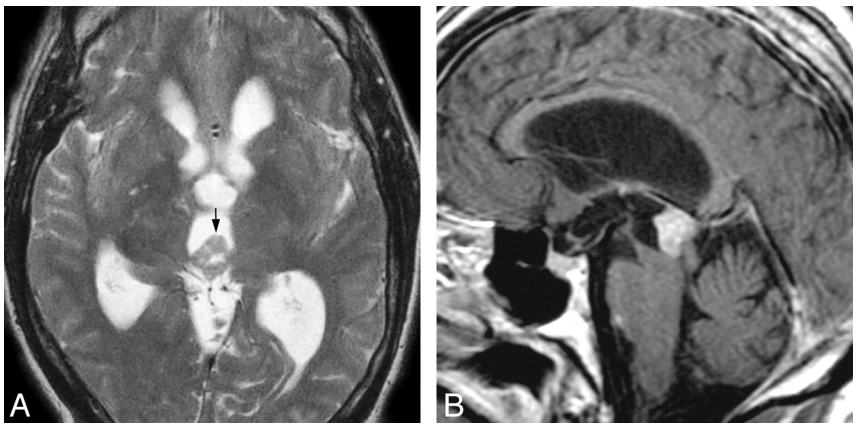

Fig 7. A 66-year-old patient who presented with headache and neck stiffness. *A,* Axial T2WI shows a well-delineated mixed iso-/hyperintense lobulated mass in the pineal region (*arrow*). *B,* Sagittal postcontrast T1WI shows that the mass enhances intensely. Papillary tumor of the pineal region was documented at pathologic examination.

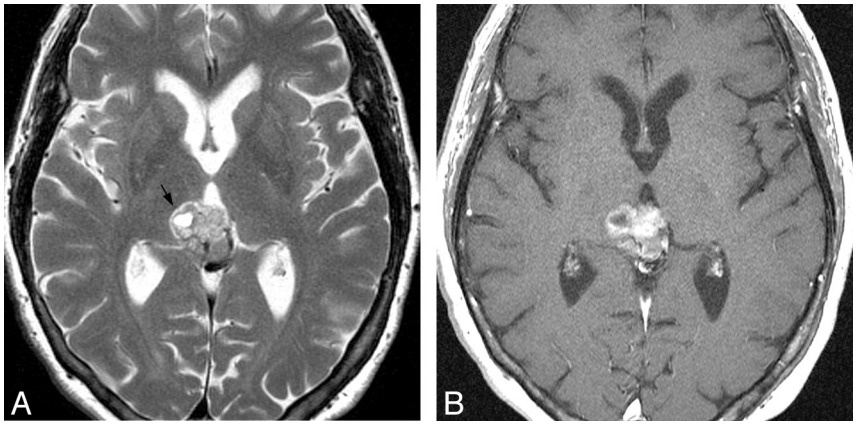

Fig 8. A 57-year-old woman who presented with Parinaud syndrome. *A,* Axial T2WI shows a large mixed hyperintense mass with focal invasion of the right thalamus (*arrow*). *B,* Axial T1WI after contrast administration shows that the mass enhances strongly but inhomogeneously. Preoperative diagnosis of PPTID was confirmed at histologic examination.

to-moderate mitotic activity result in either WHO grade II or III. PPTIDs have a much more aggressive course than pineocytomas and may warrant adjuvant therapy.

PPTIDs are more common than previously recognized, accounting for up to 20% of all pineal parenchymal neoplasms.[21,22] Recent reports emphasize their large size and focal invasion of adjacent structures as features that distinguish them from pineocytoma. Hemorrhage and cysts are common (Fig 8).

So what can the neuroradiologist really say? A moderately large, focally invasive, and strongly but heterogeneously enhancing pineal mass in a middle-aged or older adult is most likely a PPTID. PTPR or atypical pineocytoma should also be included in the differential diagnosis. PPTIDs have a significantly more aggressive course than pineocytoma, so any atypical-appearing pineal mass in an adult warrants preoperative imaging of the entire neuraxis.[21]

Poorly Differentiated and Embryonal Tumors

In 2000, ATRT was added to the category of poorly differentiated embryonal tumors. Desmoplastic and large cell MB variants were also added as defined MB variants. In 2007, two new variants were added to the MB category (ie, extensively nodular and anaplastic variants). Recent evidence suggests that MB subtypes may also have distinctly different developmental origins.[23]

MBEN. MBEN was previously termed "cerebellar neuroblastoma." MBENs are generally tumors of infants and very young children. They exhibit a markedly expanded lobular architecture and are strongly associated with cancer predisposition syndromes such as nevoid basal cell carcinoma and Li-Fraumeni and Fragile X syndromes. Although all MBs are designated as WHO grade IV neoplasms, biologically different MB entities warrant risk-adapted treatment.[24] MBENs generally have a more favorable outcome compared with classic MB.[25] After treatment, some MBENs may undergo further maturation to tumors dominated by ganglion cells.[1]

So what can the neuroradiologist really say about MBENs? MBENs may be indistinguishable from classic MB. However, a noncalcified midline posterior fossa hyperattenuated nodular mass on noncontrast CT is highly suggestive of the diagnosis. Occasionally, a marked grapelike appearance of multiple coalescing nodules can be seen on contrast-enhanced MR images and may suggest the diagnosis (Fig 9).

Anaplastic MB. At first glance, "anaplastic MB" is a somewhat confusing term. All MBs, by definition, should be anaplastic. Although all MBs show some degree of atypia, these features are particularly pronounced and widespread in anaplastic MB. Increased nuclear size and pleomorphism are typical. Anaplastic MBs have considerable histologic overlap with large cell MB, another variant.

There are very few imaging reports that distinguish the MB

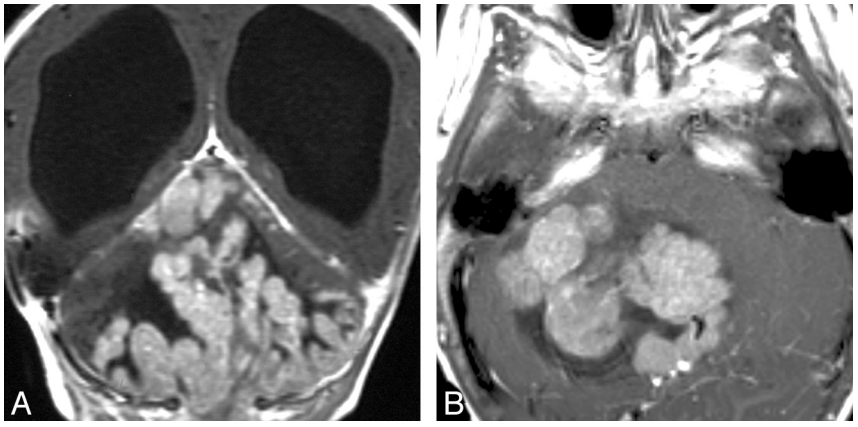

Fig 9. Two different cases of medulloblastoma with extensive nodularity are illustrated. *A,* Coronal T1C+ image in a 10-month-old infant shows strong enhancement of grapelike nodules in a huge posterior fossa mass. MBEN was diagnosed at pathology. Case courtesy of B. Jones, MD. *B,* A child with headaches and papilledema has a grossly nodular enhancing mass in the right cerebellum. Histologic diagnosis was MBEN.

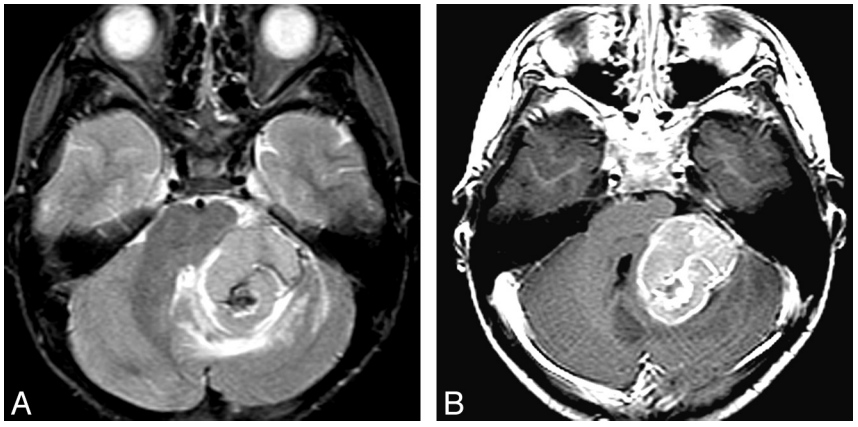

Fig 10. A 5-year-old child with surgically proved anaplastic MB. *A,* Axial T2WI shows a large mostly isointense mass in the left cerebellar hemisphere. *B,* T1C+ image the mass enhances intensely but somewhat heterogeneously. Case courtesy of S. Blaser, MD.

subtypes and variants. A recent study by Fruehwald-Pallamar et al[26] examined whether differentiation between classic MB and MB variants was possible. They found patient age was helpful because both MBEN and the desmoplastic MB variant were more common in younger children (mean age, 4.2 years), while classic MB and anaplastic variants occurred in older children and adults (mean age, 9.1 years). Almost 80% of the classic MBs were midline tumors, located in the region of the fourth ventricle. MB variants, especially the desmoplastic and MBEN types, often occurred off-midline. The off-midline location was especially prominent in adults. Classic MBs were hyperintense on T2WI while iso- or hypointensity was more commonly seen in MBENs. Approximately one-third of the classic MBs showed minimal or subtle enhancement, while all their MB variants enhanced strongly (Fig 10). The MBEN variant cases all showed multifocal homogeneously enhancing grapelike tumor nodules. Diffusion-weighted imaging showed a lower apparent diffusion coefficient for MBEN and the desmoplastic variants compared with classic and anaplastic MBs. MR spectroscopy showed typical high choline and low *N*-acetylaspartate for all MBs, classic and variants.

So what can the neuroradiologist really say? With the exception of anaplastic MB, off-midline location is more common with variant MBs. Grapelike nodularity strongly suggests MBEN, especially when seen in an infant or young child.

Tumors of the Sellar Region

The *WHO 2007* classification redefined and clarified pituicytoma, distinguishing it from granular cell tumor of the neurohypophysis. One completely new tumor entity, SCO of the adenohypophysis, was added to the grouping "neoplasms of the sellar region."

Pituicytoma. Pituicytoma was redefined as an astrocytic tumor that presumably arises from pituicytes in the posterior pituitary or stalk. True pituicytomas are rare neoplasms, with only 35 cases in the literature meeting current histologic criteria.[27,28] On imaging studies, pituicytomas are well-circumscribed, solid intrasellar (20%), suprasellar (40%), or combined (40%) lesions. Only 25% of pituicytomas can be clearly separated from the pituitary gland on MR imaging. Pituicytomas are isointense with brain on T1WI and are generally hyperintense on T2WI. Most pituicytomas enhance strongly and uniformly (Fig 11*A*). Patients with a pituicytoma present with symptoms similar to those of other sellar lesions (ie, visual changes, hypopituitarism, headache, or hyperprolactinemia related to infundibular mass effect).[4] They rarely recur, even after subtotal resection.[4,27,28]

Granular Cell Tumor of the Neurohypophysis. Granular cell tumor of the neurohypophysis, added in the *WHO 2000* update, is an intra- and/or suprasellar mass that arises from the neurohypophysis or infundibulum. Endocrine dysfunc-

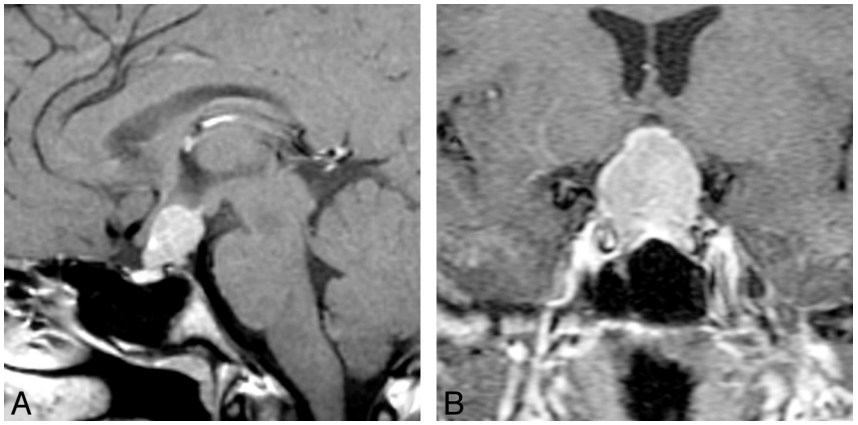

Fig 11. Newly recognized sellar region tumors are illustrated. *A,* Sagittal T1C+ image in a 22-year-old woman with hypopituitarism shows a well-delineated strongly enhancing infundibular mass that is clearly separate from the pituitary gland below. Pituicytoma. *B,* Sagittal T1C+ scan in a 69-year-old patient with headaches and bitemporal hemianopsia has an enhancing sellar/suprasellar mass that has enlarged the sella. Preoperative diagnosis was macroadenoma. Histologic diagnosis was SCO. Case courtesy of P. Hildenbrand, MD.

tion, headache, and visual disturbances are the common presenting symptoms. Granular cell tumors are most common in middle-aged adults, with a mean age of 49 years. Very few cases with imaging findings have been reported.[29,30] Granular cell tumors are typically well-delineated, usually homogeneously enhancing suprasellar masses.

SCO of the Adenohypophysis. Oncocytes are large mitochondrial-laden epithelial cells with a very acidophilic granular cytoplasm. SCO is a rare nonadenomatous oncocytic tumor of the anterior hypophysis that follows a benign clinical course. SCO is seen exclusively in adults (mean age, 56 years). Few tumors with imaging findings have been reported.[31,32] Most reported cases present as intrasellar masses with suprasellar extension. Both clinical and radiologic features are indistinguishable from nonfunctioning pituitary macroadenomas (Fig 11*B*). Grossly, SCO is also indistinguishable from conventional pituitary macroadenoma.

So what can the neuroradiologist really say about these 3 entities? When a suprasellar tumor in a middle-aged or older adult clearly arises from the pituitary stalk, rostral to—and clearly separated from—a normal pituitary gland, granular cell tumor, SCO, and pituicytoma are all diagnostic possibilities. Distinguishing pituicytoma from granular cell tumor and SCO is probably not possible on the basis of imaging findings alone. Moreover, because most pituicytomas cannot be clearly separated from the pituitary gland, macroadenoma, hypophysitis, lymphoma, granulomatous disease, and metastases are also diagnostic considerations when a sellar/suprasellar enhancing mass that involves the infundibular stalk is identified on imaging studies. Endocrinologic findings are probably more helpful in distinguishing pituicytoma from adenomas. While pituicytoma sometimes causes hypopituitarism, it almost never causes diabetes insipidus. Diabetes insipidus suggests that the correct diagnosis is not any of these rare sellar entities.

Conclusions

The *WHO 2007* classification of CNS tumors delineated a number of new tumor entities and variants. Three years later, when can the neuroradiologist say something reasonable about these neoplasms? Most are uncommon and are often indistinguishable from statistically more common entities. However, we offer several scenarios in which a preoperative diagnosis of one of these new tumors or variants may be possible. 1) An aggressive-appearing pineal mass in a middle-aged adult is more likely to be a PPTID than a "garden variety" pineocytoma. 2) Imaging findings of an unusual-appearing fourth ventricular tumor in a young or middle-aged adult should suggest the diagnosis of RGNT. 3) An aggressive-looking, H-shaped hypothalamic mass in an infant is likely to be a PMA—especially if hemorrhage is present. 4) A posterior fossa mass in a child with distinct strongly enhancing grapelike nodules is likely a MB with extensive nodularity—especially if it occurs off-midline.

Disclosures: Karen Salzman: *Consultant*: Amirsys, *Details:* Add cases to the teaching files. Review and edit educational content. *Ownership Interest:* Amirsys, *Details*: Stockholder. Anne G. Osborn: *Ownership Interest*: Amirsys, Amirsys Publishing, *Details:* shareholder, *Other Financial Interests:* CEO, Amirsys Publishing Inc.

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