

2016 Updates to the WHO Brain Tumor Classification System: What the Radiologist Needs to Know¹

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Abbreviations: ATRT = atypical teratoid/rhabdoid tumor, CNS = central nervous system, FLAIR = fluid-attenuated inversion recovery, GBM = glioblastoma, HPC = hemangiopericytoma, IDH = isocitrate dehydrogenase, NOS = not otherwise specified, SFT = solitary fibrous tumor, 2HG = 2-hydroxyglutarate, WHO = World Health Organization

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Radiologists play a key role in brain tumor diagnosis and management and must stay abreast of developments in the field to advance patient care and communicate with other health care providers. In 2016, the World Health Organization (WHO) released an update to its brain tumor classification system that included numerous significant changes. Several previously recognized brain tumor diagnoses, such as oligoastrocytoma, primitive neuroectodermal tumor, and gliomatosis cerebri, were redefined or eliminated altogether. Conversely, multiple new entities were recognized, including diffuse leptomeningeal glioneuronal tumor and multinodular and vacuolating tumor of the cerebrum. The glioma category has been significantly reorganized, with several infiltrating gliomas in children and adults now defined by genetic features for the first time. These changes were driven by increased understanding of important genetic factors that directly impact tumorigenesis and influence patient care. The increased emphasis on genetic factors in brain tumor diagnosis has important implications for radiology, as we now have tools that allow us to evaluate some of these alterations directly, such as the identification of 2-hydroxyglutarate within infiltrating gliomas harboring mutations in the genes for the isocitrate dehydrogenases. For other tumors, such as medulloblastoma, imaging can demonstrate characteristic patterns that correlate with particular disease subtypes. The purpose of this article is to review the changes to the WHO brain tumor classification system that are most pertinent to radiologists.

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Explain how brain tumor classification systems have evolved and why the 2016 WHO update represents a significant advance.
- Describe the genetic factors currently used in brain tumor diagnosis, as well as their relevance to treatment and prognosis.
- Identify areas in which radiologists may be able to influence diagnosis and treatment in patients with primary brain tumors.

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Introduction

The World Health Organization (WHO) central nervous system (CNS) tumor classification system provides a common nosologic system for clinicians, researchers, and patients when discussing primary CNS tumors. Although the various types of tumors are often learned as though they represent a fixed list, in reality the classification system necessarily evolves with our increasing knowledge of tumor pathogenesis. In recent years, a great deal has been learned about the molecular and genetic origins of brain tumors, and in 2016 WHO updated its primary brain tumor classification schema to directly incorporate

TEACHING POINTS

- In the updated 2016 WHO CNS tumor classification system, some tumors are defined by a combination of microscopic morphologic and molecular and genetic factors, whereas others continue to be defined by morphology alone.
- For the WHO 2016 revision, IDH mutation has become definitional for infiltrating gliomas in adults, with 1p/19q codeletion further characterizing the type. Oligodendroglioma is an infiltrating glioma that carries both IDH mutation and 1p/19q codeletion (which does not occur in the absence of IDH mutation). Astrocytoma is an infiltrating glioma that is subdivided in the classification by the presence of IDH mutation and never contains 1p/19q codeletion.
- Although IDH mutants themselves do not present a clear radiologic signature, 2HG can be detected at MR spectroscopy.
- Given their shared genetic features, SFT and HPC have been combined under the common name SFT/HPC, which can be classified as WHO grade I, II, or III.
- Trends have been noted in localization of tumor subtypes, including *WNT*-activated tumors centered in the cerebellar peduncle or cerebellopontine angle, *SHH*-activated tumors within the rostral cerebellar hemisphere, and group 3 and 4 tumors located at the midline. However, these are generalizations or tendencies rather than rules.

genetic information for the first time (1). We review the key changes to the WHO primary brain tumor classification system, with special emphasis on those most relevant to radiologists.

CNS Tumor Classification

The origins of the modern CNS tumor classification system can be traced to Bailey and Cushing (2), who published their seminal work *A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis* in 1926. In the following years, a number of competing CNS tumor classification systems emerged that divide tumors by morphology at microscopy. WHO published the first edition of its CNS tumor classification system in 1979, and it has since become the standard used throughout the world (3).

Before the 2016 update, the WHO CNS classification system was based solely on factors that could be assessed at microscopy. Although a tremendous amount of knowledge regarding the molecular and genetic basis of tumors was available, it was used descriptively, rather than being incorporated directly into the definitions of tumors. In the updated 2016 WHO CNS tumor classification system, some tumors are defined by a combination of microscopic morphologic and molecular and genetic factors, whereas others continue to be defined by morphology alone. It is likely that the current trend toward increasing use of molecular and genetic factors in tumor defini-

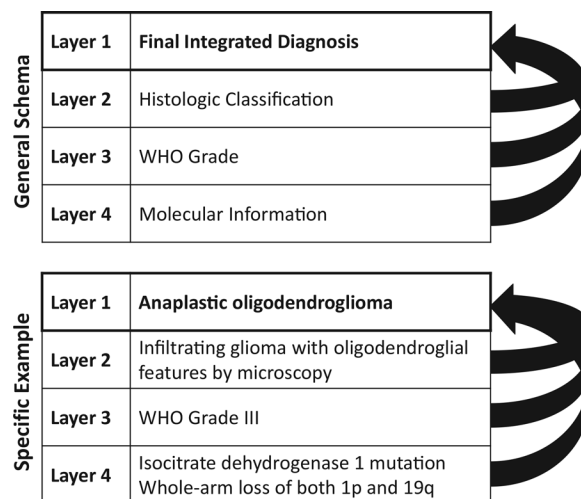


Figure 1. Layered diagnosis of CNS tumors. Integrated diagnosis (layer 1) comes last, only after layers 2–4 are defined. WHO grading criteria (layer 3) and relevant molecular information (layer 4) are separately defined for different histologic tumor types.

tion will continue, both for CNS tumors and for tumor classification more generally.

Layered Diagnosis

Under the new WHO classification schema, molecular and genetic data supplement rather than displace histologic classification. To convey all of the separate but intertwined categories of information, a group of expert neuropathologists proposed the concept of the layered diagnosis for CNS tumors (4). Although this is not part of the WHO classification itself, which does not specify how tumor designations should be reported, it has become the standard way to systematically report CNS tumor diagnoses. Figure 1 outlines the four layers. Layer 2 is the histologic classification. Layer 3 is the WHO tumor grade, defined by specific criteria for each tumor type. Under previous iterations of the WHO criteria for CNS tumors, layers 2 and 3 would have been sufficient to assign a specific tumor diagnosis. Both of these layers are primarily determined at microscopy and should be assessable with minimal delay at most institutions. Layer 4 contains the relevant molecular and genetic features, such as mutations in *IDH1* and *IDH2* (which we refer to collectively as isocitrate dehydrogenase [IDH] mutation) or 1p/19q codeletion in the case of infiltrating glioma. Finally, layer 1 is the integrated diagnosis: a summation of the molecular and morphologic data into the single diagnostic entity that best describes the tumor.

Infiltrating Glioma in Adults

Of all the changes to the WHO system for 2016, the classification system for infiltrating gliomas

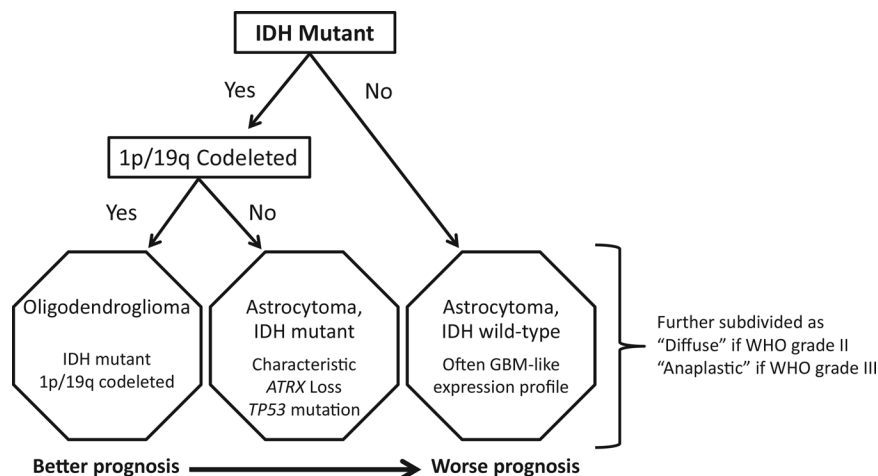


Figure 2. Diagnostic schema for WHO grades II and III infiltrating gliomas in adults.

is arguably the most significant. Previously, infiltrating astrocytomas were classified in a way that implied that they were more closely related to circumscribed astrocytomas such as pilocytic astrocytomas than to oligodendrogliomas. In the WHO 2016 classification, this comparison has been reversed, reflecting our current understanding of tumor pathogenesis.

Before the 2016 revision, the vast majority of infiltrating gliomas fell into one of three categories: astrocytomas, oligoastrocytomas, and oligodendrogliomas. The distinction was made morphologically, with classic histologic features such as chicken-wire vasculature and fried-egg cells indicating oligodendroglial tumors, for instance. These categories provided some information on prognosis, with astrocytic tumors generally being more aggressive and less responsive to chemotherapy than oligodendroglial tumors, but there was a great deal of patient-to-patient prognostic variability in this when classifying them this way. More recently, it was recognized that the concept of IDH mutations explains some of this variability, with IDH-mutant tumors carrying better prognoses than IDH-wild-type tumors (5). Likewise, a characteristic balanced translocation of the p arm of chromosome 1 with the q arm of chromosome 19, known as 1p/19q codeletion, is associated with an improved prognosis and response to chemotherapy (6).

For the WHO 2016 revision, IDH mutation has become definitional for infiltrating gliomas in adults, with 1p/19q codeletion further characterizing the type (Fig 2). Oligodendroglioma is an infiltrating glioma that carries both IDH mutation and 1p/19q codeletion (which does not occur in the absence of IDH mutation). Astrocytoma is an infiltrating glioma that is subdivided in the classification by the presence of IDH mutation and never contains 1p/19q codeletion. The previously

used diagnosis of oligoastrocytoma, which carried high interobserver variability among pathologists, is now strongly discouraged. The diagnosis of oligoastrocytoma not otherwise specified (NOS) should be used only when testing for IDH mutation and 1p/19q codeletion is not possible or has failed. Only rare tumors show both astrocytic and oligodendroglial genotypes (a so-called dual genotype) and are truly mixed tumors.

The distinction between oligodendroglioma (which is IDH mutant and 1p/19q codeleted) and astrocytoma is a clinically significant one. In the past, most WHO grade II and many WHO grade III gliomas were treated with radiation therapy alone, regardless of subtype, owing to the lack of proven benefit for chemotherapy. More recently, the combination of radiation therapy followed by chemotherapy with procarbazine, lomustine, and vincristine (PCV) has been shown to significantly improve survival in patients with WHO grades II and III gliomas harboring 1p/19q codeletion (oligodendrogliomas in the WHO 2016 definition) (7–9). Treatment with PCV also appears to improve the prognosis in IDH-mutant WHO grade II astrocytomas, although both the overall survival and relative magnitude of benefit are less than for oligodendroglioma. As such, many neuro-oncologists opt to treat patients with 1p/19q-intact gliomas with temozolomide, an alternate chemotherapeutic regimen.

Glioblastoma (GBM) is another term for WHO grade IV astrocytoma. GBM has long been informally classified into primary (approximately 90% of cases) and secondary (approximately 10%) types, on the basis of whether the tumor was thought to arise *de novo* (primary) or from progression of a previous lower-grade tumor (secondary). In addition, primary GBM generally occurred in older patients and carried a worse prognosis. With the 2016 revision, GBM is now

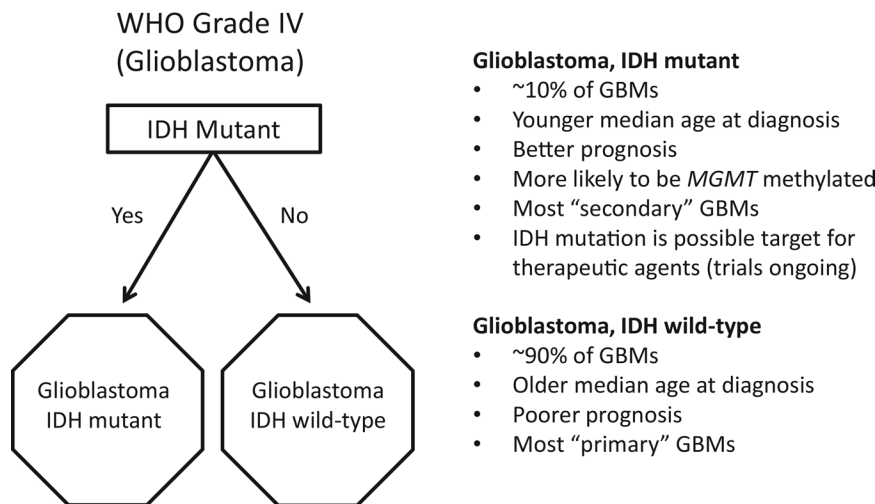


Figure 3. Diagnostic schema for GBM (WHO grade IV astrocytoma), with key features of primary and secondary tumors.

subdivided into two types on the basis of the presence or absence of IDH mutation (Fig 3). It is likely that most of the previously recognized primary GBMs were IDH wild-type, and most of the secondary GBMs were IDH mutant (10). Methylation of the promoter for *MGMT*, the gene for methylguanine methyltransferase, is well recognized as a prognostic factor in GBM (11). However, *MGMT* promoter methylation is seen in a wide variety of tumor types, so it has not become part of the definition of GBM or any other brain tumor.

Most GBMs appear at magnetic resonance (MR) imaging as peripherally enhancing necrotic lesions with surrounding T2 fluid-attenuated inversion-recovery (FLAIR) signal abnormality, which represents an admixture of infiltrating tumor and edema. Primary and secondary GBMs are generally indistinguishable at standard MR imaging. The classic imaging manifestation of GBM is a solitary ring-enhancing mass, but GBM can manifest as multifocal disease or with more unusual imaging features, as shown in Figure 4.

Mutation in *IDH1* and *IDH2* alters the role of the IDHs in the citric acid cycle and leads to accumulation of the oncometabolite 2-hydroxyglutarate (2HG) within tumor cells. Although IDH mutants themselves do not present a clear radiologic signature, 2HG can be detected at MR spectroscopy (Fig 5) (12). MR spectroscopy is a technique with which molecules can be identified and quantified at MR imaging on the basis of their characteristic resonant frequencies. MR spectroscopy of glioma often shows increased choline and lactate as well as decreased *N*-acetylaspartate and creatine relative to normal brain. Even in IDH-mutant tumors, the 2HG peak at MR spectroscopy is small relative to these other peaks, and a variety of techniques have been described to increase the conspicuity of the signal

(13). Although 2HG MR spectroscopy is currently used primarily as a research tool, routine use of this technique has been incorporated into glioma imaging protocols at some institutions. Aside from its proven impact on prognosis, preoperative identification of IDH mutation in GBM may also affect planning of therapy. Recent data suggest that resection of the tumor component that is nonenhancing at T2-weighted FLAIR imaging improves survival in patients with GBM that is IDH mutant, but not in patients with tumors that are IDH wild-type (14). MR spectroscopy for 2HG may also add value to standard MR imaging as a marker of tumor response to therapy (15). In addition, selective inhibitors of mutant IDH enzymes are currently being tested in clinical trials as targeted therapies for IDH-mutant glioma.

Recent literature suggests that 1p/19q codeletion may also be assessable at MR imaging, albeit less directly than the identification of IDH mutation at 2HG spectroscopy. It has been shown that 1p/19q codeletion is associated with characteristics such as internal heterogeneity and poorly circumscribed borders with routinely performed anatomic MR imaging sequences (eg, T1-weighted, T2-weighted, FLAIR), as well as with advanced MR imaging parameters such as apparent diffusion coefficient value and perfusion (16). The typical imaging appearance of WHO grade II oligodendroglioma is shown in Figure 6a and is compared with a well-demarcated internally homogeneous tumor that had oligodendroglial features at microscopy and IDH mutation but lacked 1p/19q codeletion and is classified as an astrocytoma by the 2016 WHO criteria. Computed tomography (CT) can also provide valuable information regarding 1p/19q codeletion. In a recent analysis of patients with suspected WHO grade II or III glioma at MR imaging, the presence of calcification at preoperative

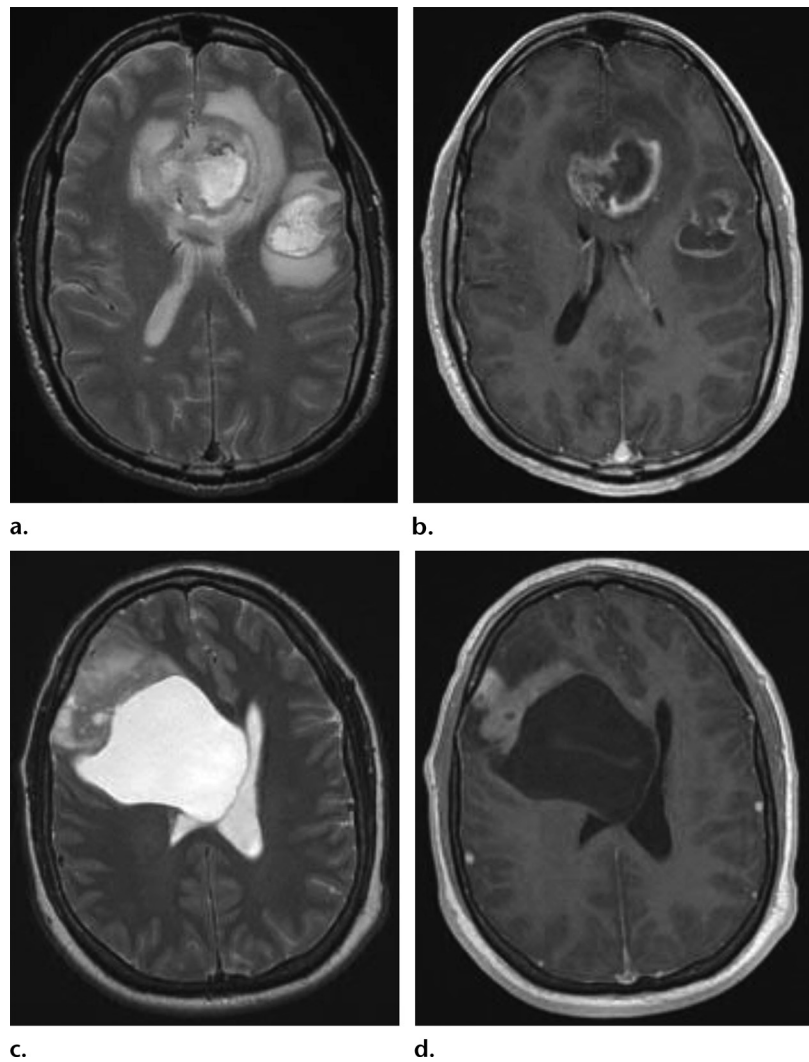
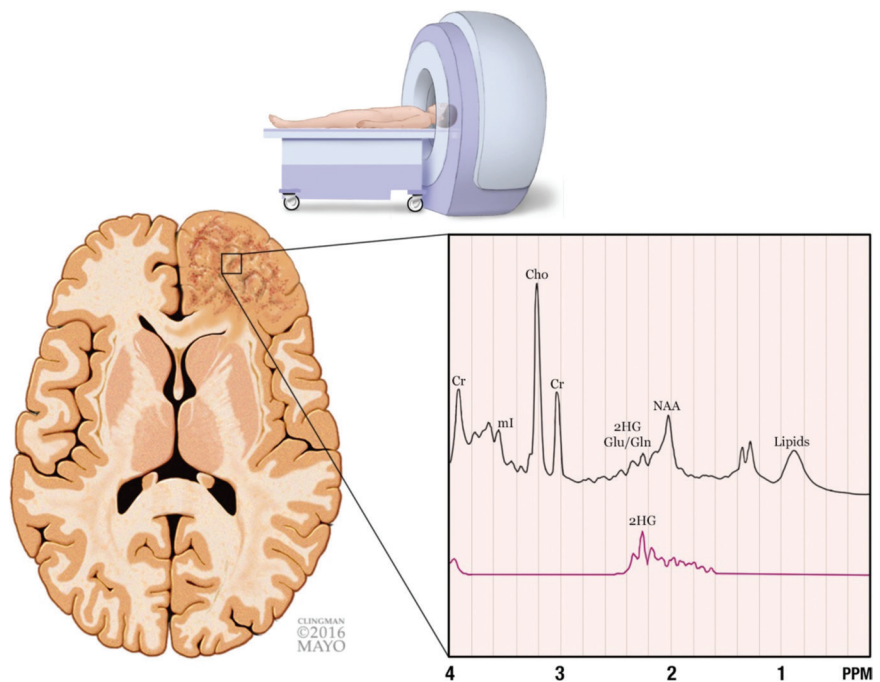


Figure 4. (a, b) Axial T2-weighted (a) and gadolinium-enhanced T1-weighted (b) MR images in an adult patient show multifocal IDH-wild-type GBM with involvement of the corpus callosum. (c, d) Axial T2-weighted (c) and gadolinium-enhanced T1-weighted (d) images in an adult patient show IDH-mutant right frontal GBM with an unusual radiologic appearance.

Figure 5. Illustration shows MR spectroscopy for identification of 2HG in gliomas with mutation of the *IDH1* or *IDH2* genes. (Reprinted, with permission, from Mayo Foundation for Medical Education and Research.)



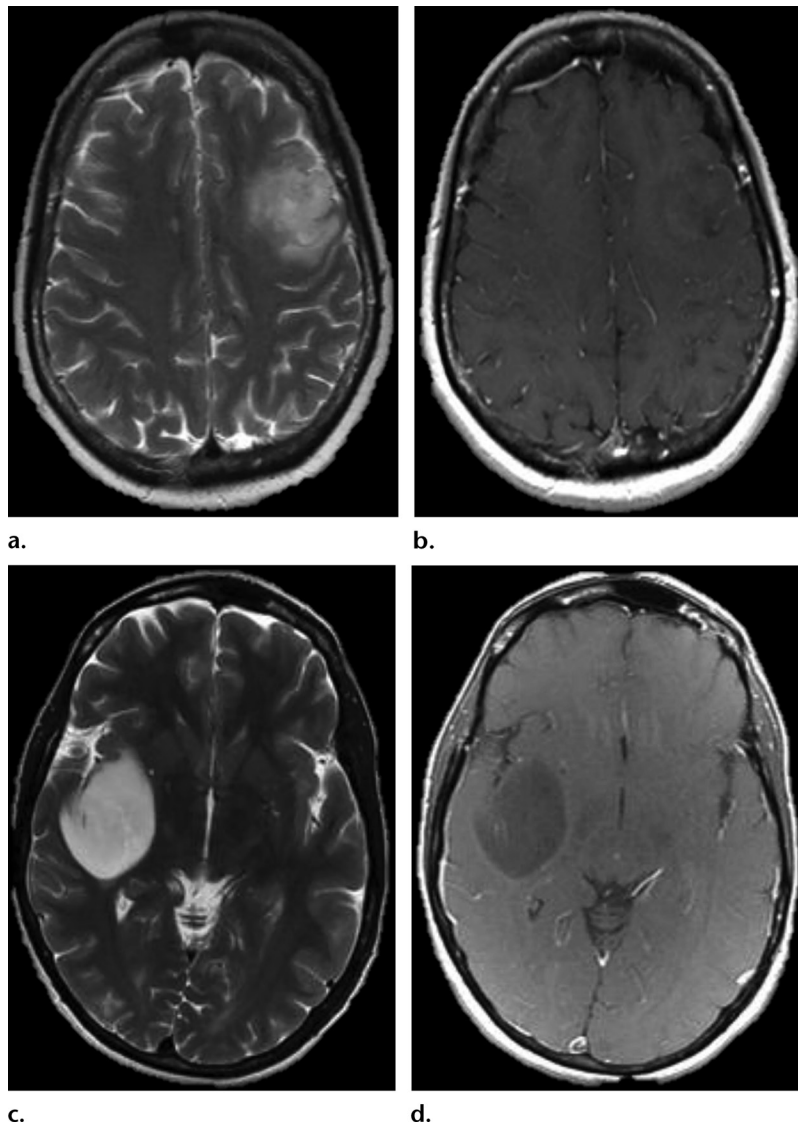


Figure 6. (a, b) Axial T2-weighted (a) and contrast-enhanced T1-weighted (b) MR images in an adult patient demonstrate a tumor with internal heterogeneity and indistinct borders, classified as WHO grade II oligodendroglioma. (c, d) Axial T2-weighted (c) and contrast-enhanced T1-weighted (d) MR images in an adult patient show a tumor with well-defined borders and internal homogeneity. The tumor demonstrated oligodendroglial features at microscopy (not shown) but lacked 1p/19q codeletion and thus is an astrocytoma according to the WHO 2016 criteria.

CT was highly associated with codeletion (17). It is often stated that while oligodendroglioma is the tumor with the highest rate of calcification, most calcified gliomas are GBMs due to their much greater overall prevalence (18), but it is not clear whether this is still true in the current WHO 2016 era. Gliomas can demonstrate a number of patterns of calcification, including but not limited to punctate foci, coarse chunks of calcium, and a ribbon pattern of calcification characteristic of oligodendroglioma (Fig 7).

Gliomatosis cerebri was previously recognized as a defined tumor entity. For 2016, it has been redefined as merely a pattern of exceptionally widespread tumor growth that can be displayed by any of the infiltrating gliomas, although it is most common in anaplastic astrocytoma. In the supratentorial compartment, the term is reserved for tumors that involve at least three cerebral lobes. Thus, the term *gliomatosis cerebri* (or simply gliomatosis) remains appropriate for use by radiolo-

gists when describing a widely infiltrating glioma. Figure 8 displays two examples of the gliomatosis cerebri growth pattern in tumors of different histologic classifications and WHO grades. Of note, although it is not part of the formal definition, many radiologists predominantly use the term *gliomatosis cerebri* to refer to nonenhancing or minimally enhancing tumors, as the vasogenic edema surrounding a GBM may have a similar appearance.

A number of areas of controversy regarding infiltrating glioma persist despite the new classification system. In particular, several inconsistencies between tumor classification and behavior remain unresolved. WHO grade III astrocytoma (anaplastic astrocytoma) that is IDH wild-type carries a worse prognosis than does WHO grade IV astrocytoma (ie, GBM) that is IDH mutant (5). Similarly, the IDH-wild-type variant of WHO grade II astrocytoma behaves far more aggressively than does the IDH-mutant version of WHO grade II astrocytoma or even

Figure 7. Oligodendroglioma in two adult patients. Axial nonenhanced CT images demonstrate characteristic ribbon-like calcification involving the right fronto-temporal (a) and left frontal (b) regions.

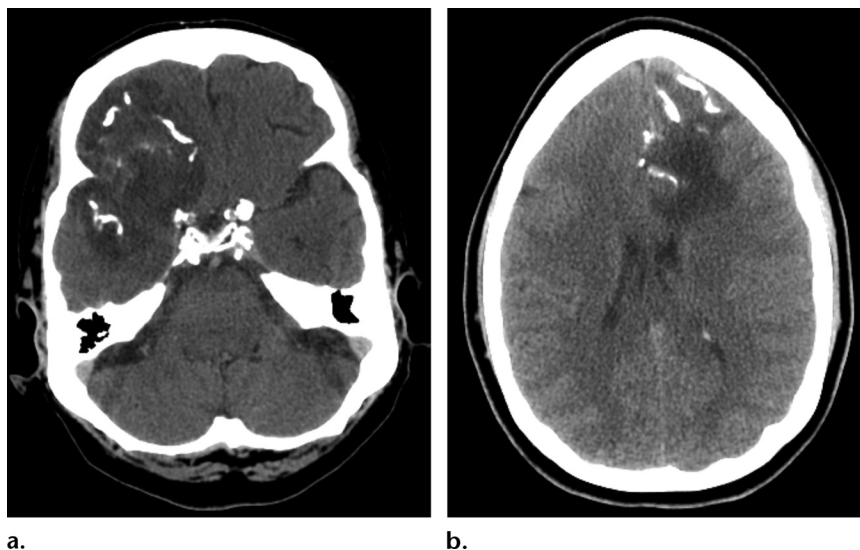
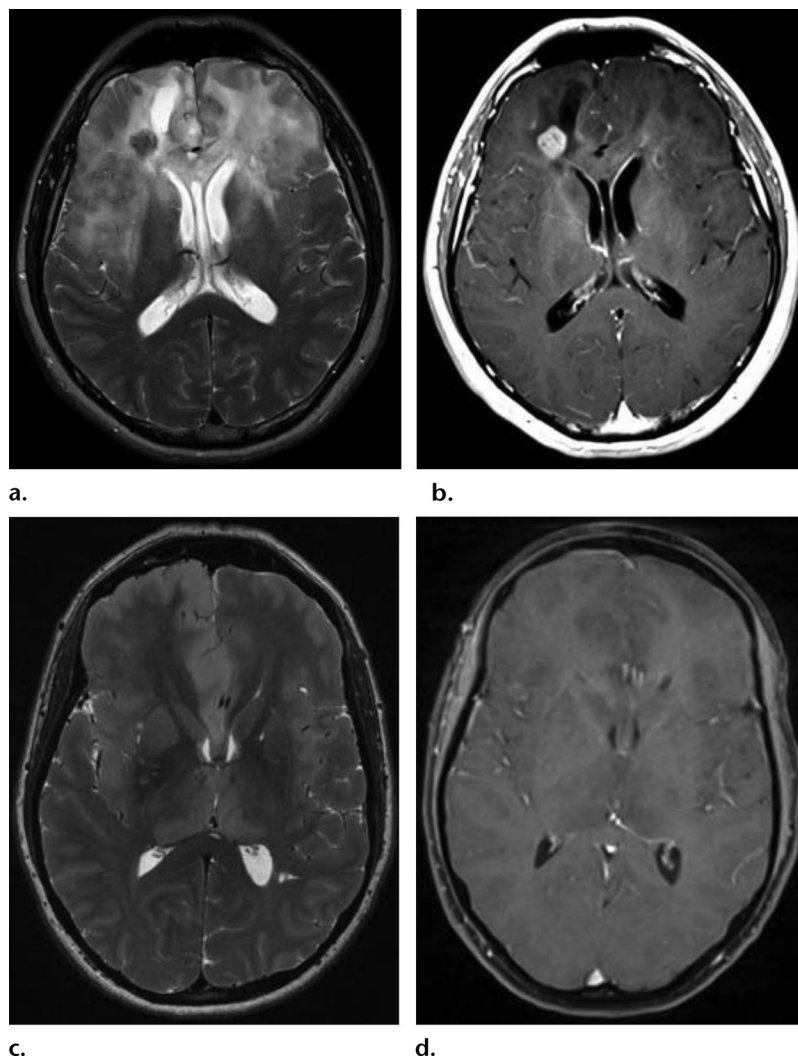


Figure 8. Gliomatosis cerebri pattern of tumor growth. (a, b) WHO grade III oligodendroglioma in an adult patient. Axial nonenhanced T2-weighted (a) and gadolinium-enhanced T1-weighted (b) MR images show extensive, predominantly bifrontal infiltration. (c, d) WHO grade II astrocytoma in an adult patient. Axial nonenhanced T2-weighted (c) and gadolinium-enhanced T1-weighted (d) MR images show frontal disease that is greater on the right than on the left, with bilateral medial thalamic involvement.



higher-grade tumors. Some experts have proposed the designation of molecular GBM for these IDH-wild-type astrocytomas regardless of the WHO grade determined at histologic

analysis. Likewise, some analyses have suggested that 1p/19q-codeleted oligodendrogliomas carry a similarly good prognosis regardless of whether they are WHO grade II or III, and that perhaps

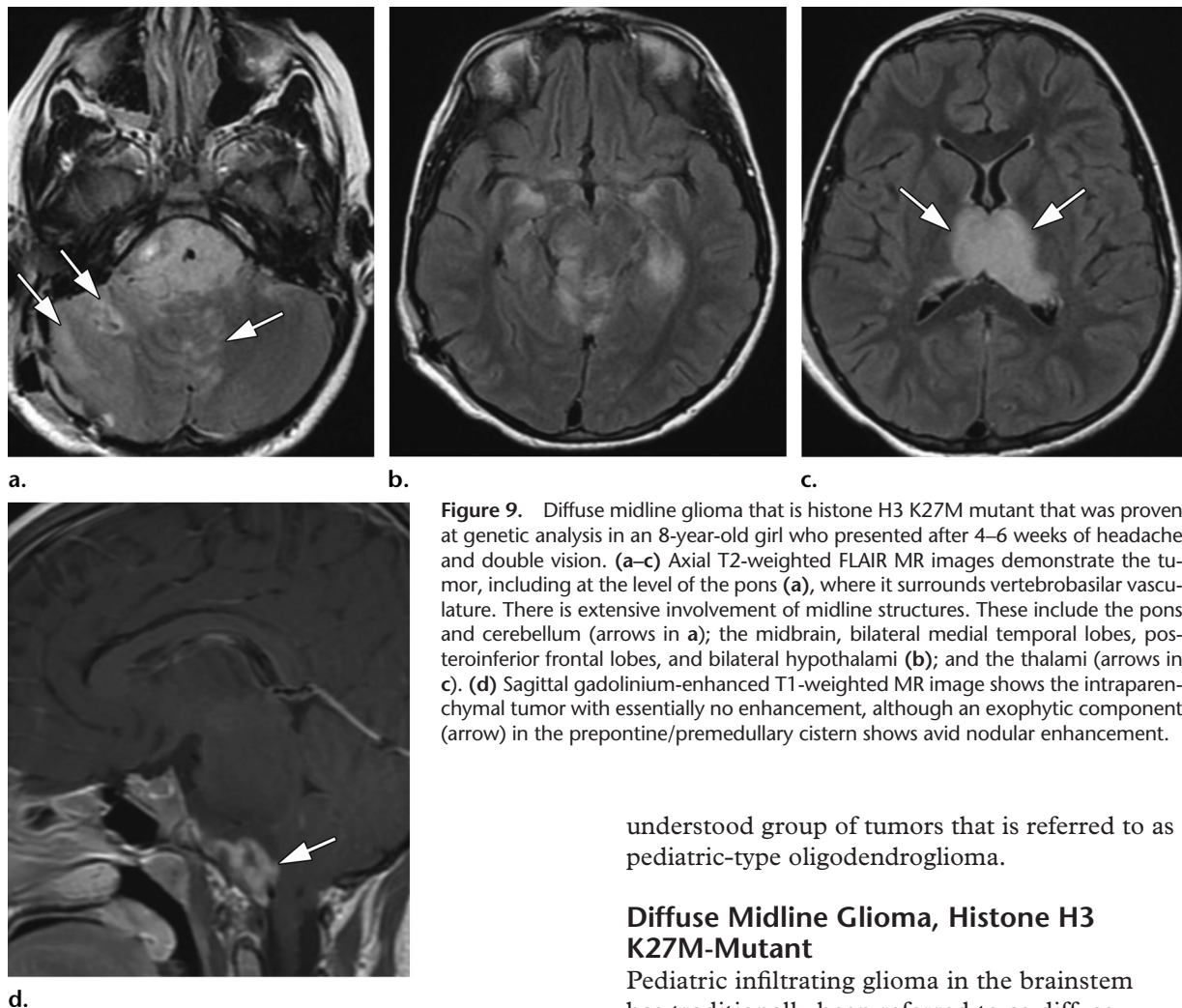


Figure 9. Diffuse midline glioma that is histone H3 K27M mutant that was proven at genetic analysis in an 8-year-old girl who presented after 4–6 weeks of headache and double vision. (a–c) Axial T2-weighted FLAIR MR images demonstrate the tumor, including at the level of the pons (a), where it surrounds vertebral basilar vasculature. There is extensive involvement of midline structures. These include the pons and cerebellum (arrows in a); the midbrain, bilateral medial temporal lobes, posterior inferior frontal lobes, and bilateral hypothalami (b); and the thalami (arrows in c). (d) Sagittal gadolinium-enhanced T1-weighted MR image shows the intraparenchymal tumor with essentially no enhancement, although an exophytic component (arrow) in the prepontine/premedullary cistern shows avid nodular enhancement.

this grade distinction should be eliminated. Neither of these proposals was adopted in the 2016 WHO update, but they remain considerations for the future.

Gliomas in Children

For many years it has been recognized that infiltrating gliomas in children behave very differently from those in adults, despite identical features at microscopy. For example, most pediatric infiltrating gliomas occur in the brainstem, whereas most adult gliomas are supratentorial. Further, pediatric gliomas carry different prognoses and respond to different chemotherapeutic regimens than do adult gliomas. More recently, it has been demonstrated that the common genetic alterations in adult infiltrating gliomas such as IDH mutation and 1p/19q codeletion are rare in children, whereas other characteristic mutations are much more common. In children, it is possible for a tumor that is a morphologically classic oligodendroglioma to lack IDH mutation and 1p/19q codeletion. This represents an unusual and poorly

understood group of tumors that is referred to as pediatric-type oligodendroglioma.

Diffuse Midline Glioma, Histone H3 K27M-Mutant

Pediatric infiltrating glioma in the brainstem has traditionally been referred to as diffuse intrinsic pontine glioma (DIPG). Because of its locally infiltrative growth pattern within a highly eloquent region of the brain, biopsy is typically avoided and diagnosis often relies on radiologic results and clinical characteristics. Recent investigations into the underlying genetic makeup of these lesions based on biopsy, surgical, and autopsy specimens have shown that approximately 60%–80% of cases harbor mutations at position K27 in the gene for histone H3 (most commonly *H3F3A*) (19–22) as opposed to 14%–22% of non-brainstem gliomas with this mutation (20,21). As a majority of DIPGs harbor this mutation, this subset has now been formally recognized as a specific tumor entity (1). The term *diffuse midline glioma* indicates that these tumors do not exclusively occur in the pons and also may be found in the thalami, cerebellum, spinal cord, and other midline structures, including the third ventricle, hypothalamus, and pineal region (1,22,23). Figure 9 demonstrates the propensity of diffuse midline glioma to involve midline structures (22).

The classic imaging appearance of a pediatric DIPG is a large, expansile, asymmetric mass

with its epicenter in the pons and with variable infiltration into the midbrain, medulla, brachium pontis, and cerebellum. There is often exophytic spread laterally and ventrally with basilar artery encasement (24). At MR imaging, the lesion is T2 hyperintense with possible intratumoral hemorrhage and necrosis. Enhancement is typically minimal, usually involving only a quarter of the tumor volume (25). A recent series of 33 patients with DIPG showed that those with the histone H3 K27M mutation had variable imaging appearances. The study found no significant differences in characteristics of enhancement, infiltration, or peritumoral edema in patients with DIPG with or without the mutation (20). For pontine lesions, patients typically have rapid onset of brainstem deficits and hydrocephalus, specifically presenting with a clinical triad of cranial neuropathies, long-tract signs, and ataxia (1,24). Those patients with tumors arising in the thalamus present instead with hemiparesis, motor deficits, and gait instability (23,26).

The majority of histone H3 K27M-mutant tumors are high-grade astrocytomas with high proliferative potential (20,21,23,27), often with contiguous extension of tumor from the brainstem into the thalami and upper cervical spinal cord (1,27,28). Distant discontinuous supratentorial spread as far as to the frontal lobes has been observed and can create a gliomatosis cerebri appearance (1). Leptomeningeal spread of disease is not uncommon; in a study that reviewed autopsy material or biopsy and/or surgical specimens from 44 cases of DIPG, approximately one-third had leptomeningeal spread (27). Despite the variability of morphology and histologic grade with DIPG, the presence of the K27M mutation designates the tumor as grade IV even in the absence of other morphologic high-grade features. Although the K27M mutation tends to confer a worse prognosis in brainstem midline gliomas, a recent study found no significant difference in overall survival between patients with K27M-mutant and wild-type thalamic gliomas (29). The K27M mutation in the histone H3 gene has been found to be commonly associated with *TP53* overexpression, although it is mutually exclusive with *IDH1* mutation and *EGFR* amplification (22).

Solitary Fibrous Tumor and Hemangiopericytoma

Solitary fibrous tumor (SFT) and hemangiopericytoma (HPC) were previously categorized as different tumor types, the former a WHO grade I benign tumor and the latter a tumor of more variable behavior that included both WHO grades II and III varieties. Over the last several years it has become clear that despite their clinically discrep-

ant behavior, these tumors share a fundamental genetic feature, namely the common genomic inversion at the 12q13 locus, fusing the *NAB2* and *STAT6* genes. Given their shared genetic features, SFT and HPC have been combined under the common name SFT/HPC, which can be classified as WHO grade I, II, or III. For the most part, SFT/HPC WHO grade I is likely to be a slow-growing surgically curable tumor. SFT/HPC grades II and III will encompass most of the tumors previously called HPC and carry a higher risk for local recurrence or even systemic metastasis. Figure 10 demonstrates the potential for aggressive clinical behavior, including metastases, of WHO grade III SFT/HPC.

SFT/HPC introduces a convention to CNS tumors that has long been part of classification of tumors elsewhere in the body: the separation of tumor type and grade. For example, although meningiomas can be categorized into grades I–III, grade I is formally designated as meningioma, grade II as atypical meningioma, and grade III as anaplastic meningioma. No such qualifiers are necessary in naming SFT/HPC: they are simply SFT/HPC WHO grades I–III. Although this may seem like a subtle distinction, the decoupling of tumor name and grade could open the door for similar reorganization for other brain tumor types, such as gliomas, in future editions of the WHO classification system.

Historically, HPC was classified as a subtype of meningioma. From a pathologic and genetic standpoint, these tumors are now recognized as being unrelated, although they are often considered in the same radiologic differential diagnosis, as both can manifest as aggressive-appearing dura-based masses. Of note, the grading schema for meningiomas has been revised slightly for 2016. Beginning with the 2007 WHO revision, meningiomas with brain invasion were considered prognostically to be WHO grade II tumors given their increased likelihood of recurrence, but it was specifically noted that brain invasion could be seen in “histologically benign” meningiomas. As of 2016, brain invasion itself is sufficient grounds for formal designation of a meningioma as WHO grade II, even in the absence of other atypical features.

Embryonal Tumors

The term *primitive neuroectodermal tumor* was previously used to denote a tumor belonging to a group of highly malignant, small round-cell tumors of neuroectodermal origin that included medulloblastomas and atypical teratoid/rhabdoid tumors (ATRTs). In the latest update of the WHO classification for CNS tumors, this term is no longer included in the diagnostic lexicon.

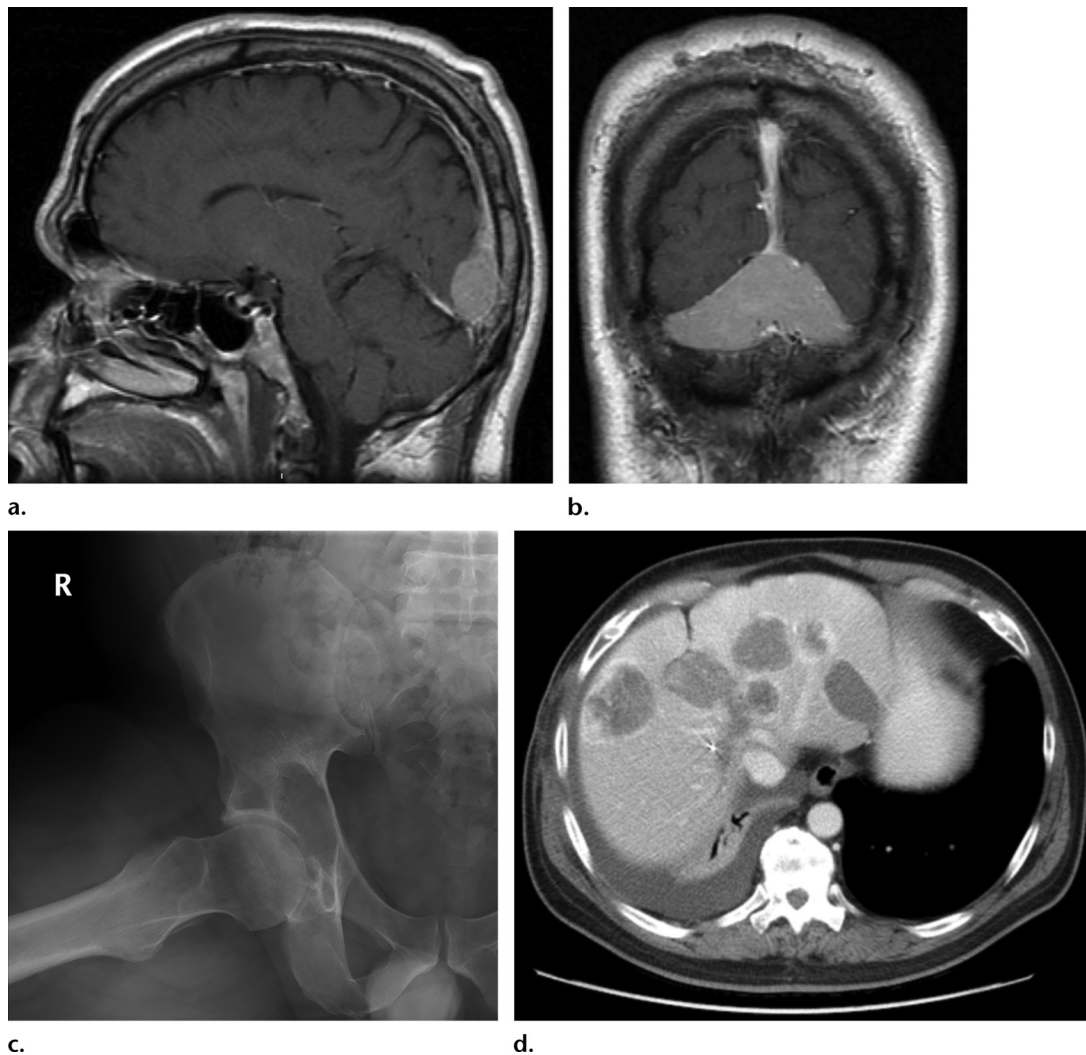


Figure 10. WHO grade III SFT/HPC tumor in an adult patient. (a, b) Sagittal (a) and coronal (b) gadolinium-enhanced T1-weighted MR images demonstrate an avidly enhancing dura-based tumor involving the torcula. (c, d) Right hip radiograph (c) and axial contrast-enhanced CT image (d) demonstrate metastases involving the right iliac bone and the liver, respectively.

Tumors in this group will now be referred to individually by name. Those that are genetically defined include medulloblastoma; ATRT; and embryonal tumor with multilayered rosettes, C19MC altered. Those not yet genetically defined include medulloepithelioma, CNS neuroblastoma, CNS ganglioneuroblastoma, and CNS embryonal tumor NOS.

Medulloblastoma

Medulloblastoma is the most common CNS embryonal neuroepithelial tumor and most common malignant solid tumor in childhood. It is characterized by a densely packed population of cells with a high nucleus-to-cytoplasm ratio and abundant mitotic figures. Medulloblastomas have historically been classified by their histologic subtype. Beyond the classic morphology, there are desmoplastic/nodular, extensive nodularity, and large cell/anaplastic (LCA)

variants. Over the past several years, integrative transcriptional profiling studies have identified underlying genetic differences in medulloblastoma. By consensus, these have been refined into four distinct genetic subtypes: *WNT*-activated, *SHH* (sonic hedgehog)-activated, group 3, and group 4. Each molecular subgroup affects specific patient demographics and is associated with differing clinical outcomes (30–33). However, an integrated approach to diagnosis of medulloblastoma that combines morphology with genetic analysis best represents the varying characteristics and prognoses of these tumors and is now encouraged.

The *WNT*-activated group comprises only 10% of the genetically defined medulloblastomas. Nearly all of the former demonstrate classic histologic features (90%), which confer an excellent prognosis in this genetic profile group (34–36). Rarely, these tumors have LCA morphology, with

a less-certain prognosis. *WNT*-activated medulloblastomas typically occur in older children and younger adolescents, ages 7–14 years. Unlike other types of medulloblastoma that arise from the cerebellum, the *WNT*-activated variety is thought to arise from cells in the dorsal brainstem (37). At MR imaging, they are thus seen closely abutting the brainstem in a midline orientation or are off center in the cerebellar peduncle or cerebellopontine angle (37–39). If centered at the foramen of Luschka, they can spread along the lateral fourth ventricle and appear intraventricularly. Hallmark genetic aberrations include *CTNNB1* mutation and monosomy 6 (32,40).

The *SHH*-activated group makes up one-third of medulloblastoma cases and is histologically variable. Those without a *TP53* mutation (representing the majority of cases) encompass nearly all desmoplastic nodular types that affect children, adolescents, and young adults, and all extensive nodularity types that mainly affect infants. These have a generally good prognosis. Rare *TP53*-mutated types have either LCA or classic morphology and carry a much worse prognosis. The *SHH*-activated tumors arise from cerebellar granule cell precursors and tend to be more centered within the cerebellar parenchyma at imaging. Some studies have found *SHH*-activated tumors frequently localized to one cerebellar hemisphere (37). A study by Teo et al (39) noted this location only in children and young adults, whereas in infants the tumor more often involved the cerebellar vermis. *SHH*-activated tumors are mostly solid and avidly contrast-enhancing masses; a grape-like nodular appearance has been described with the extensive nodularity subtype (41). Characteristic genetic markers include *PTCH1* mutation, which also predisposes patients to nevoid basal cell carcinoma in Gorlin syndrome.

Tumors that are neither *WNT*-activated nor *SHH*-activated are poorly differentiated, are excluded genetically from the previously mentioned groups, and are designated as either group 3 or 4 medulloblastomas. Together, they account for about 60% of medulloblastomas. Tumors in both groups have mostly classic histology, manifest in childhood, and are often metastatic at presentation, particularly so for group 3 (30,32). *MYC* amplification is a primary feature of group 3 medulloblastomas seen mostly in infants that confers a poor outcome (42). Although classic histology predominates, group 3 encompasses most of the LCA morphology, which also portends a poor prognosis. Both groups 3 and 4 are typically located at midline. Group 3 has been associated with ill-defined margins and extensive enhancement. Group 4 has been associated with relatively absent or scant enhancement (38,43).

Trends have been noted in localization of tumor subtypes, including *WNT*-activated tumors centered in the cerebellar peduncle or cerebellopontine angle, *SHH*-activated tumors within the rostral cerebellar hemisphere, and group 3 and 4 tumors located at the midline. However, these are generalizations or tendencies rather than rules. *WNT*- and *SHH*-activated tumors are particularly more variable and may be seen in midline locations as well. Figure 11 demonstrates characteristic MR imaging appearances for each of the four medulloblastoma subtypes.

Atypical Teratoid/Rhabdoid Tumors

ATRTs are highly aggressive embryonal tumors of the CNS seen primarily in children younger than 3 years. Although by definition they contain rhabdoid cells, ATRTs have widely divergent cell populations, including mesenchymal, epithelial, glial, and neuronal cell lines accounting for the “teratoid” descriptor (44). Nearly all ATRTs demonstrate biallelic inactivation of *SMARCB1* (or *INI1*) on chromosome 22, whereas a very small percentage show inactivation of *SMARCA4* (or *BRG1*) (45). Having one of these genetic alterations is now formally required for diagnosis (1). In those tumors that have histopathologic features consistent with ATRT but with absence of the genetic marker, or where genetic testing is unavailable, a descriptive diagnosis alone may be used (1).

ATRTs may be infratentorial or supratentorial (46). In the posterior fossa, they are most often within the cerebellum or brainstem in an off-midline position. Tumors situated in the cerebellopontine angle have been reported (47). Supratentorially, they may be hemispheric or intraventricular. Leptomeningeal dissemination is common, occurring in 15%–20% of cases (48–50).

ATRTs are often large and heterogeneous, with children presenting with an enlarging head circumference and vomiting that are due to resulting obstructive hydrocephalus and mass effect, respectively. Solid portions of these masses are hyperattenuating at CT and may be slightly hypointense at T2-weighted MR imaging with restricted diffusion because of their dense cellularity. These imaging features classically mimic those of other embryonal tumors such as medulloblastoma when the tumor is located in the posterior fossa. Potential distinguishing features from medulloblastoma include intratumoral hemorrhage, prominent necrotic regions, and occasional calcifications (47–51). Heterogeneous enhancement is typical. A reported but nonspecific enhancement pattern is a thick wavy band of enhancement surrounding a cystic/necrotic center (46,51). There is typically relatively

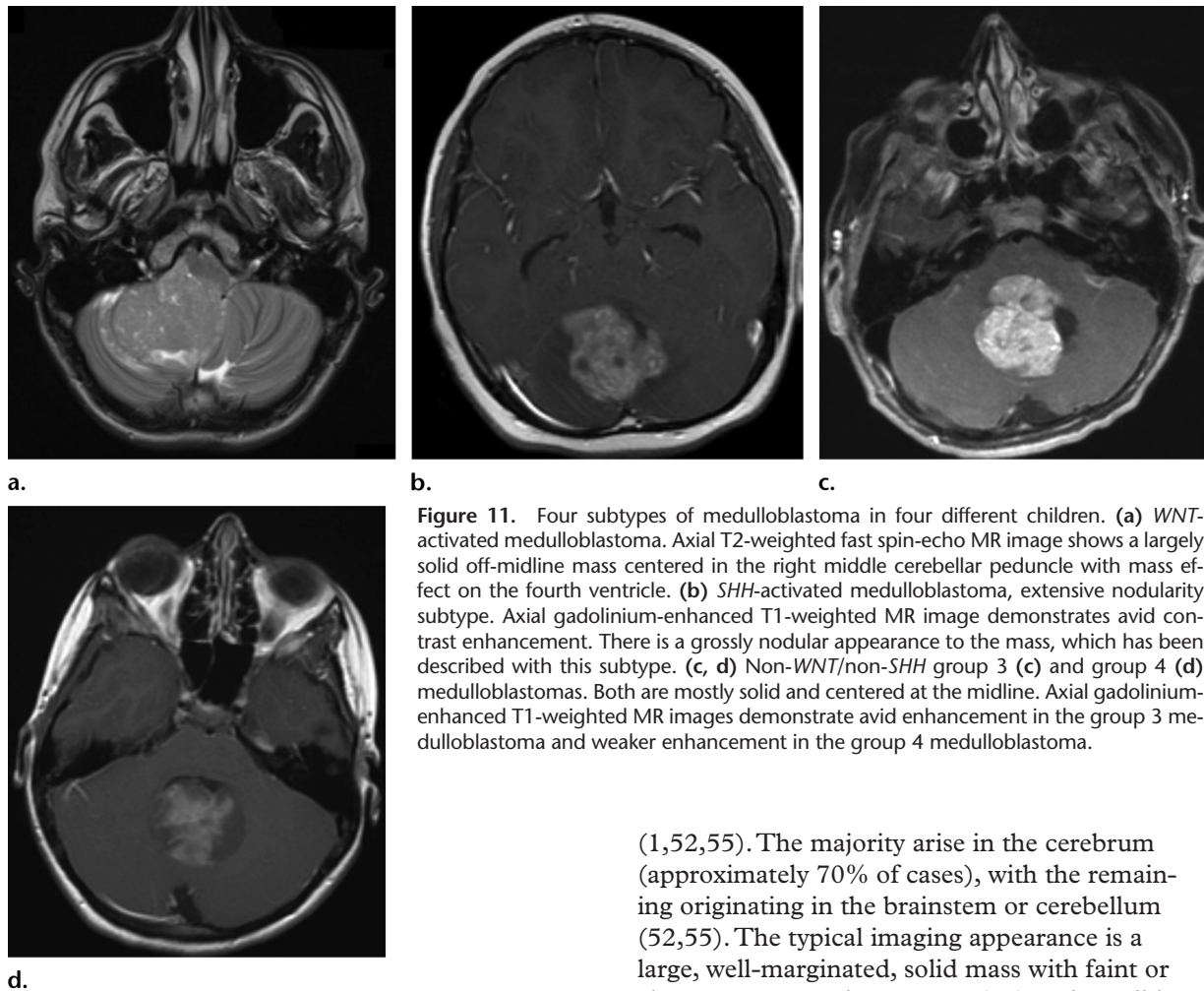


Figure 11. Four subtypes of medulloblastoma in four different children. (a) *WNT*-activated medulloblastoma. Axial T2-weighted fast spin-echo MR image shows a largely solid off-midline mass centered in the right middle cerebellar peduncle with mass effect on the fourth ventricle. (b) *SHH*-activated medulloblastoma, extensive nodularity subtype. Axial gadolinium-enhanced T1-weighted MR image demonstrates avid contrast enhancement. There is a grossly nodular appearance to the mass, which has been described with this subtype. (c, d) Non-*WNT*/non-*SHH* group 3 (c) and group 4 (d) medulloblastomas. Both are mostly solid and centered at the midline. Axial gadolinium-enhanced T1-weighted MR images demonstrate avid enhancement in the group 3 medulloblastoma and weaker enhancement in the group 4 medulloblastoma.

little edema for the size of the tumor. Figure 12 shows two examples of ATRTs.

Embryonal Tumor with Multilayered Rosettes, C19MC-altered

CNS embryonal tumors with multilayered rosettes include tumors previously classified as embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma. Common histopathologic features of these tumors include small, blue, neuroectodermal tumor cells forming multilayered ependymoblastic rosettes in a background of neoplastic neuropil (52). Recent genome-wide analyses revealed alterations at 19q13.42 within the C19MC locus in a majority of these tumors, indicating that they may represent variations of a single entity (52–55). Due to this shared genetic marker, any CNS embryonal tumor harboring C19MC alterations should now be diagnosed as embryonal tumor with multilayered rosettes, C19MC-altered, regardless of whether it exhibits characteristic histopathologic features (1).

These tumors invariably affect only children younger than 4 years, most commonly infants

(1,52,55). The majority arise in the cerebrum (approximately 70% of cases), with the remaining originating in the brainstem or cerebellum (52,55). The typical imaging appearance is a large, well-margined, solid mass with faint or absent contrast enhancement (52) and possibly cysts or calcification. Figure 13 demonstrates a posterior fossa C19MC-altered tumor. Metastases to leptomeninges have been described as nodular and cohesive deposits showing persistence of both small blue-cell tumor and neoplastic neuropil components at histologic analysis (56). The differential diagnosis includes other CNS embryonal tumors, desmoplastic infantile ganglioglioma, and anaplastic ependymoma.

Commonly reported symptoms are related to increased intracranial pressure and include headaches, nausea, vomiting, and visual disturbances. Movement disorders can be seen with infratentorial tumors (52) and are more likely evident in older children. The disease course is aggressive and the prognosis is nearly always dismal; one series of 29 patients reported a mean survival of 9 months (52).

New Tumors and Patterns

Diffuse Leptomeningeal Glioneuronal Tumor

A rare glioneuronal neoplasm with characteristic extensive leptomeningeal involvement was previously called both disseminated oligodendroglioma-like leptomeningeal neoplasm and primary

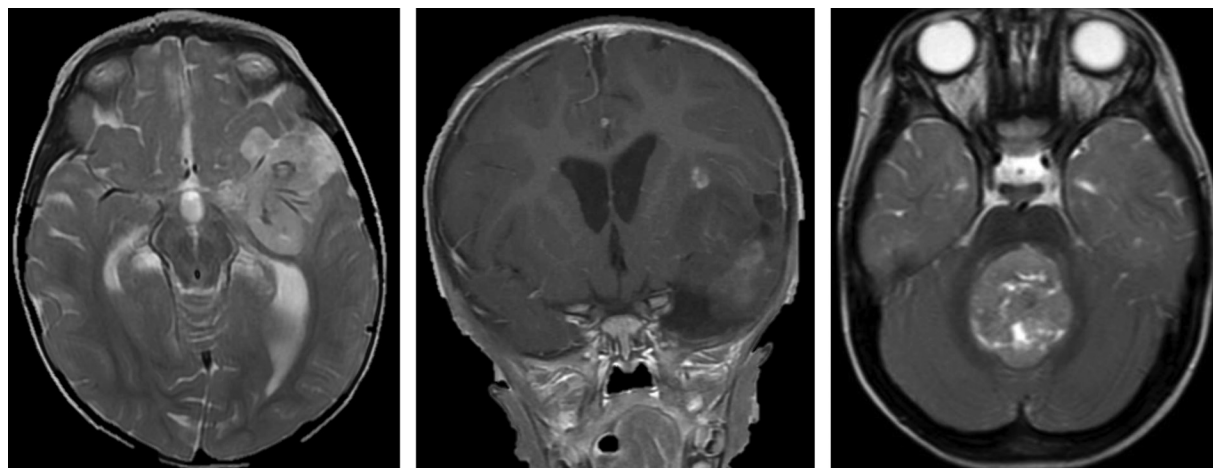
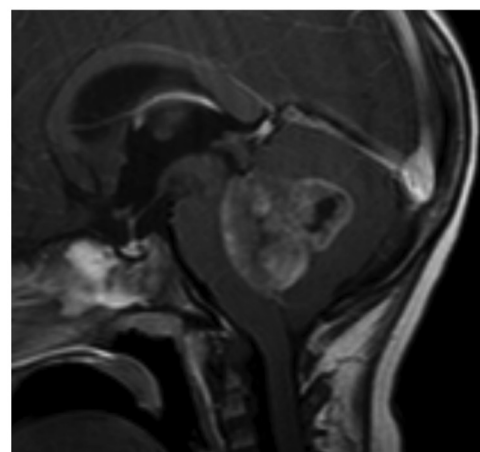


Figure 12. Two examples of ATRT. (a, b) Supratentorial ATRT in a 13-month-old female infant. Axial T2-weighted fast spin-echo (a) and coronal gadolinium-enhanced T1-weighted (b) MR images show a predominantly solid supratentorial ATRT within the left frontotemporal region with both heterogeneous signal intensity and enhancement. (c, d) Posterior fossa ATRT in a child. Axial T2-weighted fast spin-echo (c) and sagittal gadolinium-enhanced T1-weighted (d) MR images show a posterior fossa ATRT with heterogeneous T2 signal hyperintensity, patchy enhancement, and some central necrosis. With some sequences, this finding greatly resembles a medulloblastoma.

leptomeningeal oligodendrogliomatosis due to monomorphic oligodendroglial-like tumor cells seen at histologic analysis. Such entities have now been termed *diffuse leptomeningeal glioneuronal tumor*, which is recognized as a distinct tumor. It is seen mainly in children. At imaging there is readily detectable, diffuse, plaque-like and enhancing subarachnoid tumor predominantly along the spinal cord, with frequent involvement of the posterior fossa, brain stem, and basilar cisterns as well as sylvian and interhemispheric fissures (57–59). Small cystic or nodular T2-hyperintense lesions that can be seen superficially along the parenchymal surface represent expansion and fibrosis of subarachnoid spaces (58,60). Figure 14 demonstrates the key features of two examples of this tumor at MR imaging. Associated distinct intraparenchymal tumors are reportedly more typical in the spinal cord than in the brain; 81% of the largest studied cohort (31 patients) had such intramedullary spinal cord lesions (58).

Because of its frequent involvement of the posterior fossa and basal brain, diffuse leptomeningeal glioneuronal tumor can resemble chronic inflammatory meningitis (61), and there may be obstructive hydrocephalus at presentation (62). At histologic analysis, oligodendroglial-like cells show low mitotic activity (58). Clinically, most are slowly progressive. These findings suggest that this is a low-grade entity. However, because of its rarity, there are insufficient data to designate a distinct WHO grade at this time (1). The genetic profile supports a



d.

glial lineage with markers that overlap with but are distinct from oligodendroglioma and neurocytoma (63–65).

Ependymoma, *RELA* Fusion–Positive

Ependymomas can occur in the cerebrum, posterior fossa, or spinal cord. Until recently, grading criteria for ependymomas across age groups and locations have been based solely on histopathologic analysis in a one-size-fits-all approach. Although ependymomas can appear the same histologically, emerging data have shown they may have substantially different molecular features.

The most common structural marker found in ependymomas is fusion of the *C11orf95* and *RELA* genes (66–68). This is found in approximately 70% of all childhood supratentorial tumors and is absent in posterior fossa or spinal cord ependymomas (68). WHO has now defined a type of supratentorial ependymoma based on the presence of this fusion of *C11orf95* with *RELA*. Within this group, histopathologic analysis shows varying degrees of anaplasia, although most are WHO grade II or III. As with other genetic markers, its presence could potentially

Figure 13. Embryonal tumor with multilayered rosettes, C19MC altered, situated in the posterior fossa, in a 12-month-old male infant. The tumor was proven at genetic analysis. **(a)** Sagittal post-gadolinium T1-weighted MR image shows a large, solid, well-defined mass with little to no enhancement. There is substantial associated mass effect and resulting obstructive hydrocephalus. **(b)** Apparent diffusion coefficient map demonstrates central areas of restricted diffusion.

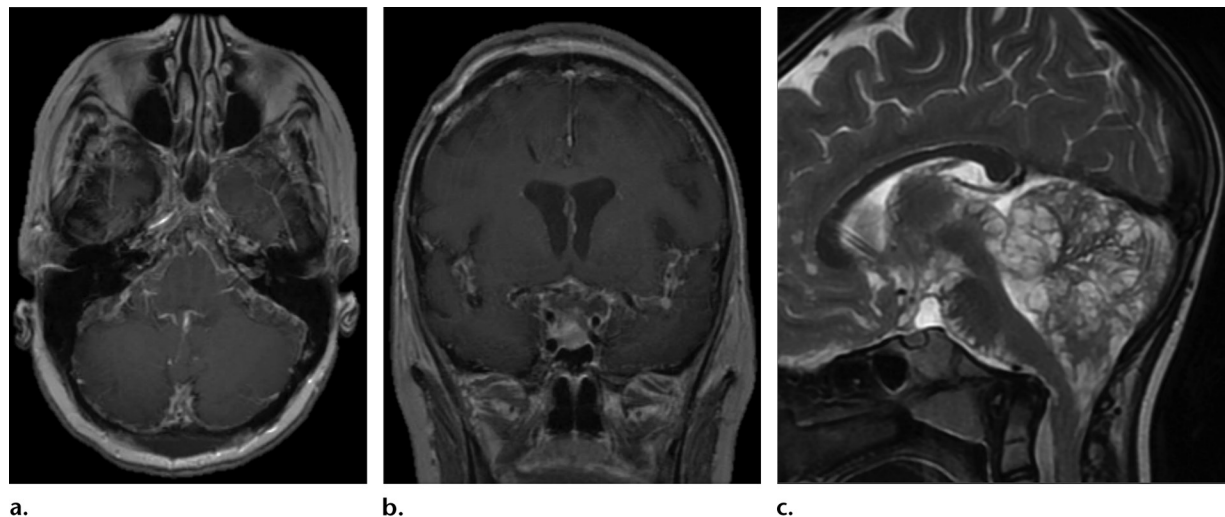
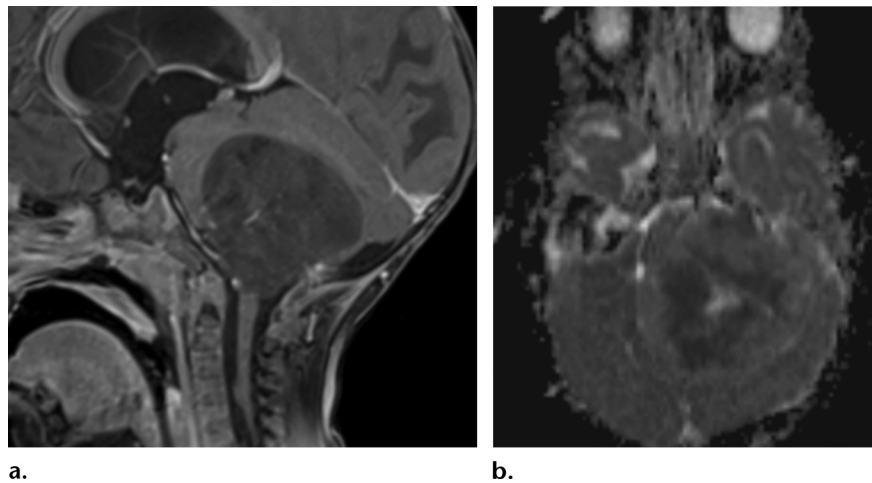
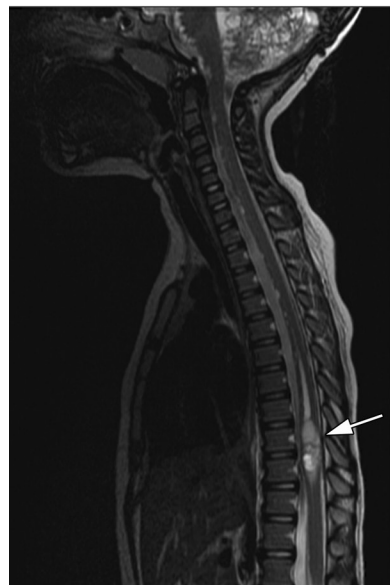


Figure 14. **(a, b)** Diffuse leptomeningeal glioneuronal tumor in a 45-year-old woman. Axial **(a)** and coronal **(b)** gadolinium-enhanced T1-weighted MR images show this process throughout the brain, greatest in the posterior fossa and sylvian fissure. **(c, d)** Diffuse leptomeningeal glioneuronal tumor in a 4-year-old girl. Sagittal T2-weighted fast spin-echo MR image of the brain **(c)** demonstrates extensive subpial and cortical cystic nodules involving the cerebellum, pons, and midbrain and the basilar subarachnoid spaces. Sagittal T2-weighted fast spin-echo MR image of the thoracic spine **(d)** shows a multicystic mass (arrow) within the spinal cord with an associated syrinx. Multiple tiny cystic structures are seen along the surface of the entire cord.

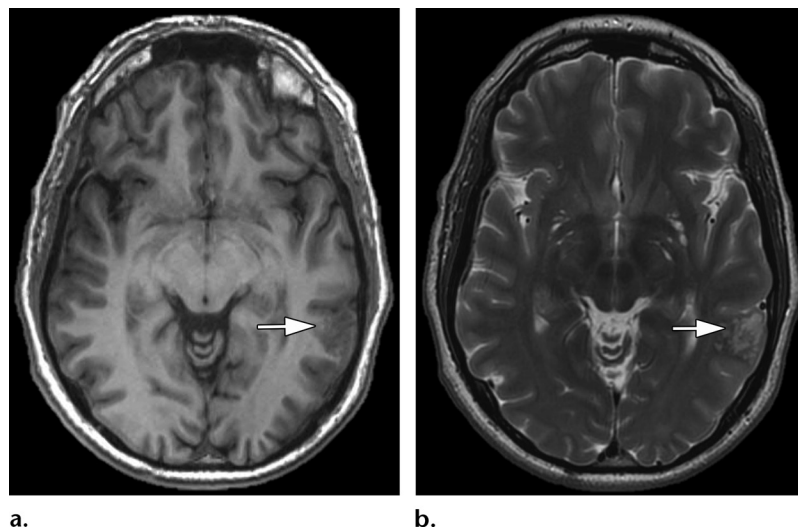


serve as a target for therapy (68). Although this is currently the only formally genetically defined ependymoma in the WHO guidelines, other studies have shown several molecular subgroups

in each CNS compartment by using DNA methylation profiling (67), as well as specific epigenomic alterations that define hindbrain ependymomas (69). Additional genetically defined ependymomas are likely forthcoming.

Both supratentorial and infratentorial ependymomas predominantly occur in children ages 1–5 years, with a smaller peak of supratentorial tumors seen in young adults 20–30 years of age. At imaging, supratentorial tumors tend to manifest as large hemispheric solid and cystic masses in both children and adults. Solid components are more likely to show increased diffusion restriction and perfusion compatible with a high-grade tumor (70). This is in distinction to the soft/plastic slow-growing infratentorial

Figure 15. Multinodular and vacuolating neuronal tumor of the cerebrum in a 45-year-old man. Axial T1-weighted (a) and T2-weighted (b) MR images demonstrate a bubbly T1-hypointense and T2-hyperintense lesion (arrow) in the posterior left temporal lobe that is nonenhancing.



ependymomas that have relatively low cellularity and usually no restricted diffusion.

Multinodular and Vacuolating Neuronal Tumor of the Cerebrum

This provisional entity, which may be related to ganglion cell tumors, was mentioned in the recent WHO 2016 revision, although a specific class assignment remains unclear because of its rarity (71). Of the reported cases, most have been located in the temporal lobe and associated with seizures (71–73). At MR imaging, multinodular and vacuolating tumors of the cerebrum are T2-hyperintense nodular lesions with little if any enhancement. At histopathology, cells are arranged in nodules within the deep aspect of the cortex and/or subcortical white matter and have characteristic intracellular and stromal vacuolation (71). Overall, these appear to have a benign behavior and could even be malformative in nature. Figure 15 is an example of this tumor type proven at pathologic analysis. The differential diagnosis at imaging includes dysembryoplastic neuroepithelial tumor, ganglioglioma, and hamartoma.

Future Steps

The standardization of glioma categorization and grading under the WHO system has been extremely beneficial, as it allows patients, physicians, and researchers around the world to share a common language for treatment and research. However, there are drawbacks to this system. WHO is responsible for similar efforts across numerous different tumor types and customarily updates each of the tumor classification systems in a prescribed order rather than on an as-needed basis. As a result, many years may pass between editions, even if significant knowledge regarding tumor pathogenesis accumulates in the interim.

Exactly this situation prompted the 2016 WHO update as a revision to the 2007 edition rather than as a further-reaching new edition. This ad hoc solution is not ideal for repeated use, as would be anticipated to be necessary given the rapid pace of our expanding understanding of CNS tumors. Recently, a group named the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) (with the “NOW” acronym standing for “not official WHO”) has been formed to help remedy this situation (74). This group, initially composed largely of the collaborators on the WHO 2016 update, will evaluate possible changes to CNS tumor classification on the basis of emerging science, creating an ongoing dialogue and ideal practical consensus guidelines for practicing clinicians who deal with CNS tumors. Their recommendations would not have official standing within WHO but could potentially help to guide practice in between WHO updates and inform the update process when it occurs.

Conclusion

Recent advances in the classification of primary brain tumors have significant implications for patients and those that care for them, including radiologists. Often, the radiologist is the first physician to diagnose a probable brain tumor, and the description and differential diagnosis provided have profound implications for subsequent clinical decision making. For the first time, radiologists can noninvasively image some of the definitional features of glioma, such as IDH mutation with use of 2HG spectroscopy. It is conceivable that in the near future it will be possible to confidently identify not only IDH mutation but also 1p/19q codeletion at imaging, allowing categorization of most infiltrating gliomas in adults before surgery.

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