Updates in Pediatric Malignant Gliomas

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Abstract: Malignant gliomas constitute a smaller portion of brain tumors in children compared with adults. Nevertheless, they can be devastating tumors with poor prognosis. Recent advances and improved understanding of the genetic and molecular characterization of pediatric brain tumors, including those of malignant gliomas, have led to the reclassification of many pediatric brain tumors and new entities have been defined. In this paper, we will present some of the more recent characterization and pertinent changes in pediatric high-grade gliomas, along with the conventional and advanced imaging features associated with these entities. Implications of the recent changes in pediatric malignant glioma classifications will also be discussed.

Key Words: brain tumors, childhood brain tumors, glioma, high-grade glioma, pediatric brain tumors

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Gliomas are the most common primary central nervous system (CNS) tumors in the pediatric population.[1] Pediatric gliomas comprise a large group of tumors with variable histology, molecular biology, imaging findings, clinical manifestations, and outcome. Gliomas are further divided into 2 categories: low-grade gliomas (LGGs) and high-grade gliomas (HGGs). LGGs represent approximately 30% of all primary CNS tumors in children,[2] which are typically slow-growing lesions and classified as either grade I and II tumors. HGGs, classified as either grade III and IV, are less common and represent 15% to 20% of pediatric CNS tumors.[3]

Pediatric HGGs are typically aggressive, sharing many histologic features and poor prognosis with adult HGGs, although they often display distinct molecular and genetic features.[1,4] Pediatric HGGs may arise anywhere in the neuraxis, some with a predilection for midline or near-midline structures such as the brainstem and thalamus. Pediatric HGGs are more commonly de novo tumors than adult HGGs, in which a larger proportion develops from pre-existing lower grade tumors.[5] On the basis of histologic features alone, pediatric HGGs can be classified into either anaplastic astrocytoma (AA), in which anaplasia and increased mitotic activity are seen (grade III) or glioblastoma (GBM), in which microvascular proliferation and/or necrosis are detected (grade IV). AAs and GBMs are both malignant, diffuse, infiltrating astrocytic tumors.[6] There may be a slightly better prognosis of some pediatric HGGs compared with adults, although the prognosis is variable depending on the type and age at presentation. The prognosis of recurrent HGG is nevertheless poor; a recent 20-year meta-analysis of survival showed average cumulative progression-free survival of 3.5 months and average cumulative overall survival of 5.6 months, with a trend toward slightly increased survival in recent years.[7]

In this article, in addition to the more common classic AA and GBM, we will discuss diffuse midline gliomas, H3K27M-mutant and other rare and anaplastic versions of gliomas, such as anaplastic pilocytic xanthoastrocytoma and ependymoma. We will also provide an overview of epidemiology, molecular biology, and imaging findings of the various groups of malignant pediatric gliomas and related changes in the new classification of brain tumors.

MOLECULAR CHARACTERIZATION AND THE 2016 WHO CLASSIFICATION OF BRAIN TUMORS

Many significant changes were made to the classification of pediatric malignant brain tumors in the 2016 WHO classification of tumors of the CNS.[6,8] In this edition, the importance of molecular and genetic markers of tumors was emphasized in addition to traditional histologic features alone. Although these changes involved a large variety of both adult and pediatric benign and malignant tumors, the focus of this article is specifically on malignant gliomas. An important change in the classification system has been the removal of an important pediatric malignant tumor category, primitive neuroectodermal tumors (PNETs). The main reason was the extreme heterogeneity of tumors within this category, including some with overlap with malignant gliomas, embryonal tumors, and other rare molecularly defined tumor entities. In the past, most pediatric gliomas were typically classified in the same group as adult gliomas, but significantly different molecular features have been found. We will review some of these features.

One of the genetic and molecular advances contributing to the changing classification system has been identification of the role of histone mutations. Histones are the chief protein components of chromatin that package and condense the DNA, forming the building blocks of chromosomes. They play a role in epigenetic regulation of gene expression. A missense (substitution) mutation of lysine for methionine at position 27 in the tail of 1 of the 5 main histone proteins, histone H3 (ie, a H3K27M mutation), was first identified in pediatric HGGs in 2012.[9,10] K27M mutations may occur in relation to 2 genes, *H3F3A*, which encode the H3.3 variant and the *HIST1H3B*, which encode the H3.1 variant.[10–12] These mutations cause a decreased methylation of the histone tails of the histone H3 family proteins, altering gene expression patterns that may block glial differentiation and promote gliomagenesis.[13,14] H3K27M-mutant neoplasms have a worse prognosis than compared with the wild-type tumors.[11,15] In addition to these histone mutations, mutations in other epigenetic regulators of gene expression can also be seen in pediatric HGG, which will be discussed later in this paper.

Recently, mutations in the genes isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) have been shown in large percentages of grade II and grade III gliomas and secondary glioblastomas.[16] These mutations, however, are less common in pediatric gliomas, and most of the cases are seen in adolescents. The presence of these *IDH1/2* mutations can impair isocitrate conversion in the citric acid cycle and lead to the accumulation of abnormally high levels of D-2-hydroxyglutarate (2-HG) in tumors (Fig. 1). Excess 2-HG in tumor cells act on

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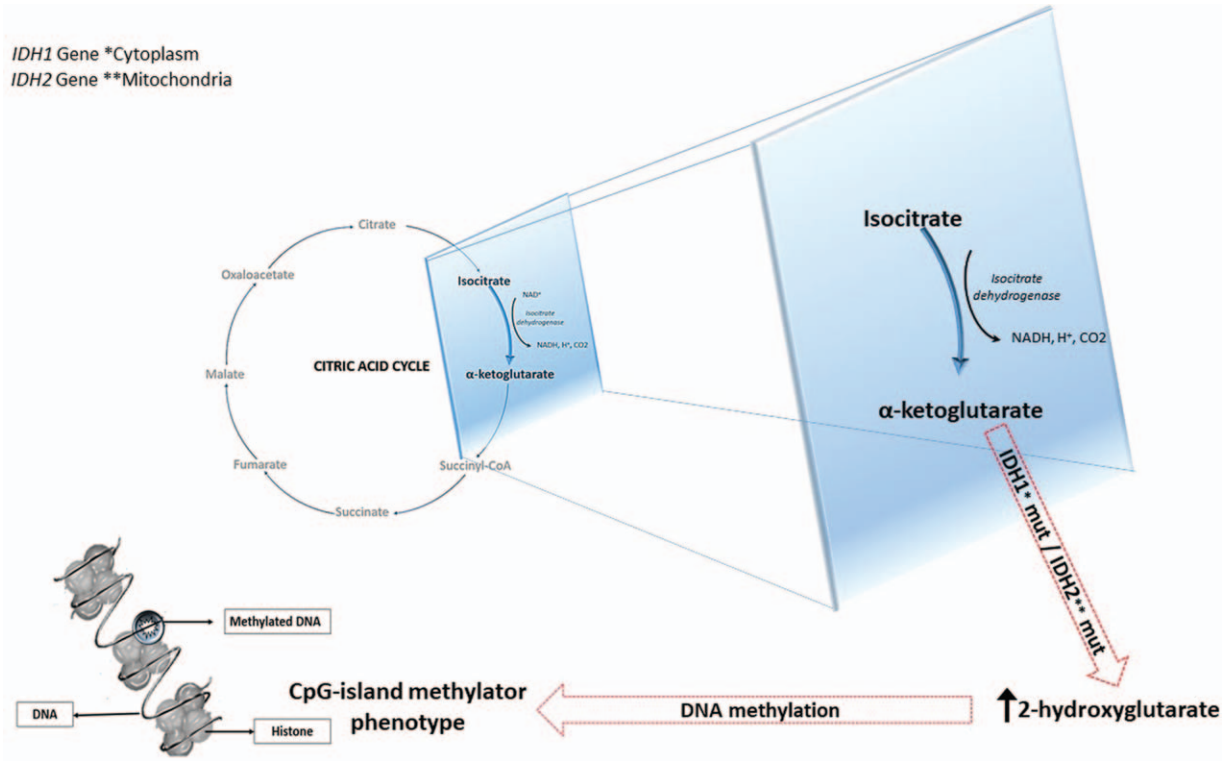

FIGURE 1. Relationship of isocitrate dehydrogenase (IDH) enzyme and IDH mutations to levels of 2-hydroxyglutarate (2HG) and DNA methylation.

normal cellular function involved in epigenetic events of histone and DNA hypermethylation, consequently blocking forms of cellular differentiation and promoting tumorigenesis.[17]

Although medulloblastomas are not considered gliomas, and therefore not the focus of this article, they are nevertheless common malignant tumors in pediatrics and with major changes to their categorization. These tumors are now classified both by their histologic features (classic, desmoplastic/nodular, MB with extensive nodularity, and large cell/anaplastic) and by their genetically defined categories (WNT-activated, SHH-activated, and non-WNT/non-SHH, which includes group 3 and group 4).[6,8] Each group has its own specific demographic, transcriptional, and resultant clinical implications.[18,19] Nevertheless, they share the feature of being composed of small, densely packed cells with high nucleus to cytoplasm ratio, hence being relatively dense on computed tomography (CT) and showing restricted diffusion on magnetic resonance imaging (MRI).

WNT-activated medulloblastomas account for about 10% of the cases. They rarely metastasize and have the best prognosis, with nearly 90% of patients surviving for more than 5 years if gross total resection is achieved and no metastatic dissemination is present at diagnosis.[20,21] SHH-activated tumors comprise approximately 25% of medulloblastomas and usually arise in the cerebellar hemispheres, as the SHH (sonic hedgehog) signaling protein is secreted by Purkinje cells, targeting the overlying external granular layer cells.[22] SHH-activated medulloblastomas are intermediate-risk tumors,[19] although they may also have *TP53* mutations that escalates the risk, as this mutation is associated with therapy resistance and frequent recurrence.[21] The cellular origin of Group 3 medulloblastomas is uncertain, but the expression of *MYC* and midline location characterizes group 3 medulloblastoma.[19,23] This group accounts for about 25% to 28% of medulloblastoma cases, with poor prognosis and high incidence of metastatic disease dissemination at diagnosis.[24] Finally, group 4 medulloblastoma represents around 35% of medulloblastoma cases.[19,23,24] They have various cytogenetic alterations, including *MYCN* amplification, *CDK6* amplification, and multiple chromosomal aberrations.[19,21,23] On imaging, these tumors are typically located within the fourth ventricle and have minimal or no contrast enhancement, possibly related to reduced vascular permeability.[25]

ADVANCED MRI TECHNIQUES IN PEDIATRIC MALIGNANT GLIOMAS

Compared with adult brain gliomas, the number of studies and evidence behind the utility of advanced MRI neuroimaging techniques is much more limited. In this section, we will provide a brief synopsis of the use and role of these techniques in the evaluation of pediatric malignant gliomas. In actuality, these techniques should serve as adjunct multiparametric imaging modalities that can work in concert for imaging evaluation of brain tumor diagnosis and follow-up.

Magnetic Resonance Spectroscopy

MR spectroscopy (MRS) may be used as an adjunct tool in the evaluation of pediatric gliomas. This technique has been applied for initial diagnosis of brain masses, biopsy guidance, tumor grading, assessment of treatment response, detection of recurrence versus treatment effects, and also as a prognostic marker in brain tumor patients. In broad terms, higher choline to creatine (Cho:Cr) and choline to N-acetylaspartate (Cho:NAA) metabolite ratios are observed in HGG than low-grade tumors and non-neoplastic masses. Myoinositol (mI) is often elevated in low-grade diffuse gliomas, whereas it is uncommon in HGGs. Elevated lipid-lactate peaks are more frequently found in HGGs, particularly in those undergoing

central necrotic changes. Mixed MRI spectral patterns can be reflective of the known heterogeneity that may be seen in many tumors.[26] Previous studies have shown that higher Cho/NAA and Cho/Cr ratios have a poorer prognosis in pediatric brain tumors.[27,28] Other studies have looked at lactate/NAA ratios and also normalized indices combining choline and lipid+lactate levels, demonstrating them to be strong correlates and predictors of outcome.[29,30]

As noted previously, mutations in the *IDH1* and *IDH2* can lead to the accumulation of abnormally high levels of D-2-hydroxyglutarate (2-HG) in certain brain tumors. This increased 2-HG level may be detected in vivo by specialized advanced spectral-edited MRS, and be used for characterization of glial neoplasms. *IDH1/2* mutations are considered prognostic biomarkers in subjects with glioma, and they are associated with longer overall survival.[31,32] A meta-analysis demonstrated excellent sensitivity and specificity of 2-HG MRS for the prediction of *IDH* mutant gliomas.[16]

A 5-metabolite MRS model (creatine, Myo-inositol, taurine, aspartate, and lipid) has been reported as being able to distinguish SHH-activated medulloblastoma from Group 3/4 tumors.[33] Group 3 and Group 4 tumors may show metabolic profiles with detectable taurine and creatine levels. On the contrary, SHH-activated tumors may show prominent choline and lipids, low creatine levels, and little or no taurine.[33]

Diffusion Imaging

Much of the literature in the application of diffusion imaging in pediatric tumors has focused on posterior fossa tumors. Nevertheless, diffusion imaging of tumors often demonstrates restricted (reduced) diffusion (low apparent diffusion coefficient, ADC) in solid portions of high-grade neoplasms with high cellular density and high nuclear-to-cytoplasm ratios. This can be observed in AA, glioblastoma, and some anaplastic ependymomas. Diffusion imaging may also aid in the differentiation of abscesses from HGGs. In a meta-analysis of diffusion imaging in pediatric brain tumor grading, both mean tumor ADC and minimum tumor ADC were able to separate low from HGGs with 96% and 83% accuracy, after the exclusion of diffuse midline gliomas.[34] In other studies, low diffusivity was shown to be associated with poor survival in diffuse pontine glioma[35,36] Similar to adult brain tumor resections, the use of diffusion tensor imaging in mapping white matter tracts may sometimes enable resection of tumors previously deemed unresectable, such as well-defined pilocytic astrocytomas in the thalami.[37]

Perfusion Imaging

In general terms, most HGGs typically show higher perfusion (cerebral blood volume, CBV and/or cerebral blood flow, CBF) than lower-grade gliomas. Nevertheless, the higher prevalence of malignant neoplasms other than gliomas and also contrast-enhancing low-grade tumors in children, as compared to adults, may confound the accuracy of grading of brain neoplasms using perfusion/permeability imaging measures.

Although dynamic susceptibility contrast (DSC) perfusion is indeed possible and feasible to perform in children, including young children,[38] the rates of injection theoretically needed to generate reliable hemodynamic parameters have often discouraged its use in very young children compared with adults and older children. There is an overall significant difference in cerebral blood volume and cerebral blood flow measures between pediatric LGG and HGG,[39] although no difference was found in permeability calculated from DSC perfusion.[36,39] Nevertheless, there is some degree of overlap between high and low-grade tumors, and this should be kept in mind in image interpretation.

A small study of patients demonstrated that dynamic contrast enhancement (DCE) perfusion could be used in aiding imaging assessment of tumor grade in pediatric brain tumors, although not all were gliomas.[40] Transfer constants from and into blood plasma (K_{trans} and K_{ep}) and extracellular extravascular volume fraction (V_e) showed a sensitivity of 71% to 76% and a specificity of 82% to 100% in separating low-grade from high-grade tumors. In another study, fractional plasma volume (V_p) was found to be significantly different between high and low-grade tumors, but K_{trans}, K_{ep}, and V_e were not statistically different. More investigation is needed in this area, with more standardized acquisition and processing methods, and with larger numbers.

It may be desirable to use arterial spin labeling (ASL) perfusion MRI in children in order to avoid potential concerns in gadolinium-based perfusion methods, such as high injection rates and recent controversial literature on gadolinium deposition. Some studies have reported similar accuracies in the differentiation of pediatric LGG and HGG using DSC and ASL perfusion techniques.[41] A meta-analysis of 8 studies assessing pediatric glioma grading using ASL showed many bias and applicability issues. For differentiation of low and high-grade tumors, the pooled sensitivity ranged from 0.69 to 0.92, and specificity ranged from 0.63 to 0.93.[42] Relative CBF demonstrated less variability than absolute CBF, as would be expected, given the variability of acquisition techniques. In another meta-analysis, normalized cerebral blood flow derived from ASL perfusion had 83% accuracy in separating low and high-grade pediatric brain tumors, although these were not all gliomas.[34]

PEDIATRIC GLIOBLASTOMAS

Glioblastomas are very aggressive WHO grade IV primary brain tumors, commonly seen in adults, but less commonly observed in children (Fig. 2). The reported incidence of glioblastomas in the pediatric population varies from 3% to 15%. It is most commonly reported in the second decade of life, although they may occur at any point during childhood.[43–45]

According to the 2016 WHO classification, glioblastomas are divided into 3 major subgroups, glioblastomas, IDH-wildtype, corresponding to the majority of the cases, glioblastomas, IDH-mutant, and glioblastomas, NOS (not otherwise specified).[6,8] Although glioblastomas have a poor outcome throughout any stage of life, a few studies have demonstrated a relatively better prognosis and long-term survival in pediatric patients.[3,44,45] Even though adult and pediatric glioblastomas share similar histopathological features,[46] there are often several differences in their molecular characteristics. The molecular profile of glioblastomas is correlated to demographics, prognosis, imaging findings, and possible treatment targets; hence, they complement histopathology for improved tumor classification. Accordingly, the common molecular characteristics of these tumors would be relevant to radiologists and neuroradiologists, along with their potential recognizable imaging patterns.

The majority of secondary HGGs (75%) are glioblastomas and may be observed many years later after CNS radiation treatment for childhood malignancies, including leukemia and other brain tumors such as medulloblastoma.[47] These are uncommon occurrences, and the average time to development of these tumors is 8.75 years.[47] The molecular profile of these secondary glioblastomas is typically different from other glioblastomas, and they generally have a very poor prognosis.

ANAPLASTIC ASTROCYTOMAS

AA is a WHO grade III malignant and diffusely infiltrating primary brain tumor, which comprises 4% of all malignant CNS tumors and 10% of all gliomas.[48] Many of these tumors are secondary to a transformation from a lower-grade astrocytoma,[49] and nearly a quarter may be a de novo tumor.[49] Similar to glioblastomas, AA is less common in children, being most frequently found in the adult

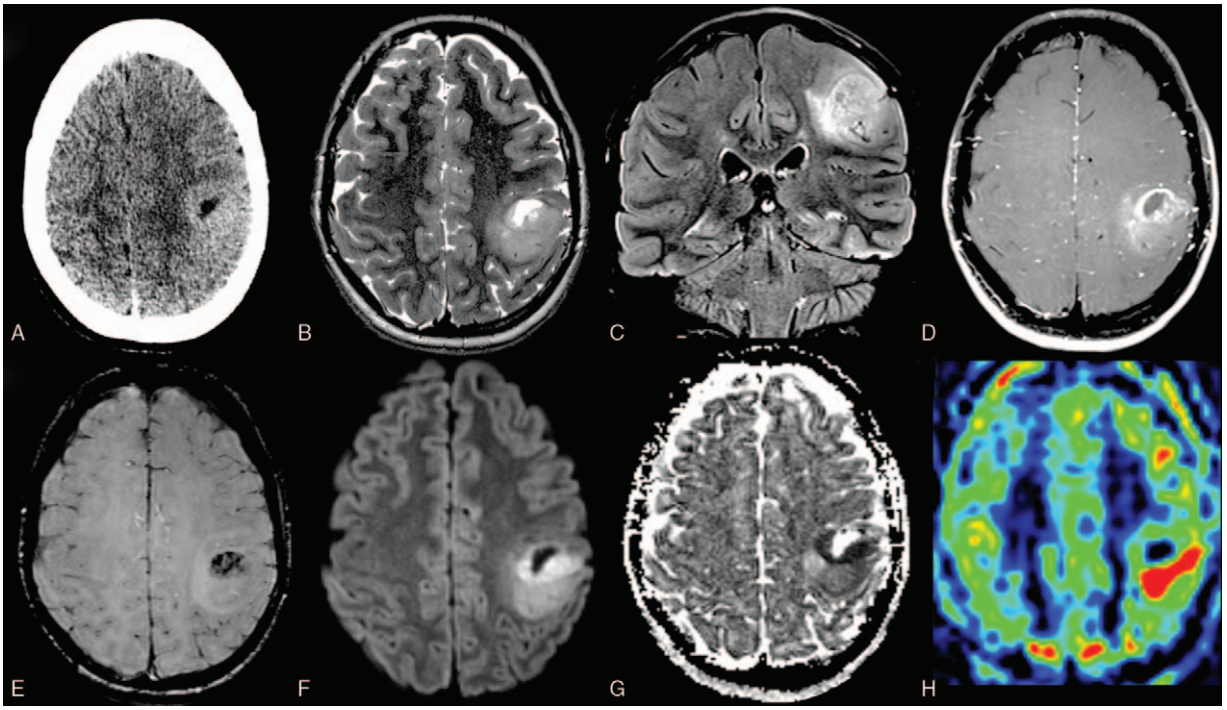

FIGURE 2. A 15-year-old female with glioblastoma, H3.3G34R mutation (grade IV). A, Axial CT image shows a heterogeneous mass with areas of hyper and hypodensity centered within the left anterior parietal lobe (A). On MRI, axial T2-weighted (B) and coronal FLAIR (C) sequences show an infiltrative and hyperintense mass located in the cortex and juxtacortical white matter. Axial contrast-enhanced T1-weighted (D) and susceptibility (E) sequences demonstrate peripheral and irregular areas of enhancement with central components of necrosis and hemorrhage. F–H, DWI, ADC, and ASL-perfusion images show the presence of restricted diffusion and elevated perfusion in the posterior part of the tumor.

population with a peak incidence between 40 and 50 years of age.[50] As such, it may be prudent that children presenting with AA undergo an investigation into an underlying cause, including exposures, genetic syndromes such as neurofibromatosis, other phakomatoses, and Li-Fraumeni syndrome (LFS), among others. Overall, these tumors have a poor prognosis (11% 5-year survival), relapsing with an average interval of 2 to 3 years, and sometimes with transformation into a glioblastoma grade IV.[51]

The key histological features which are present in AA, but absent in low-grade tumors, are nuclear atypia and higher mitotic activity rate. Unlike glioblastomas, however, AAs do not exhibit necrosis or vascular proliferation. A finding of secondary AA consists of heterogeneous areas of low- and high-grade tumor components due to the dedifferentiation from a lower grade glioma. The histologic diagnosis, however, is sometimes prone to sampling error, and accordingly, the role of molecular classification is essential for clinical decision-making.[52–55] Similar to glioblastomas, WHO grade III AA are separated into IDH-mutant, IDH-wildtype, and NOS categories. The majority of AAs belong to the IDH-mutant category when IDH testing is available.[6] The presence of the IDH mutation in AA is a favorable prognostic factor independent of age and *MGMT* promoter methylation status.[6,56,57] Moreover, AAs usually present with pathogenic variants in *TP53* and *ATRX* genes[58] and are differentiated from oligodendroglial tumors, which exhibit codeletion of chromosomes 1p and 19q.

On imaging, AA shares some features with infiltrating low-grade astrocytomas, such as grey and white matter involvement, spreading in one or more lobes, and often indistinct borders. However, heterogeneity of the signal intensity, areas of restricted diffusion, and presence of gadolinium enhancement (which implies disruption of the blood-brain barrier) are not typically observed in infiltrative low-grade astrocytomas and can be useful imaging findings. Advanced MRI methods may further assist in the evaluation of AA, as previously discussed.

DIFFUSE MIDLINE GLIOMA, H3K27M–MUTANT

Diffuse midline glioma, H3K27M–mutant is a new entity defined by both histology and molecular features, recently incorporated into the 2016 WHO Classification of Tumors of the CNS.[6,8,59] Diffuse midline glioma, H3K27M–mutant includes tumors previously described as diffuse intrinsic pontine glioma (DIPG) or diffuse brainstem glioma, but include other midline tumors as well. Detection of an H3K27M mutation in an infiltrative glioma in the midline is sufficient to classify the tumor as a grade IV neoplasm, even in the absence of microvascular proliferation or necrosis. The K27M mutation is present in the vast majority of cases of DIPG, and these children have an expected survival rate of less than 5% to 10% at 2 years following diagnosis.[3] A meta-analysis of survival in patients with the H3K27M mutations showed that these patients are 3 times more likely to succumb to their disease and lower survival by more than 2.3 years.[60] H3K27M-mutant patients have a worse prognosis than compared with the wild-type tumors.[11,15] In one study, although low diffusivity was associated with poor survival, no difference was found between H3K27M-mutated and wild-type tumors.[36]

The median age of presentation of patients with diffuse midline glioma is of 5 to 11 years, with pontine tumors occurring earlier (7 years) than the thalamic tumors (11 years), and no gender predilection.[8] Clinical presentation is variable, depending mainly

upon the location of the tumor, with common presentations, including multiple cranial neuropathies, long tract signs, ataxia, or hydrocephalus. History is usually short, including nausea, vomiting, drowsiness, nystagmus, or facial paresthesia.[61] Diffuse midline gliomas, H3K27M–mutant typically present with diffuse growth pattern, and a midline or near-midline location, including the brain stem, thalamus, hypothalamus, third ventricle, pineal region, cerebellum, and spinal cord.[12,59] The imaging features of diffuse midline gliomas with histone H3K27M mutation are highly variable, ranging from expansile masses without enhancement or necrosis with large areas of surrounding infiltrative growth to an enhancing mass with central necrosis with marked mass effect, but little surrounding T2/FLAIR hyperintensity.[59]

There are no reliable qualitative conventional imaging differences (enhancement, border, or central necrosis) between histone H3 wild-type and H3K27M-mutant diffuse midline gliomas.[59] Moreover, there were no differences reported in diffusion characteristics or ADC histogram parameters between mutant and wild-type tumors.[36] A meta-analysis of diffusion and perfusion in pediatric brain tumors found that diffuse midline glioma was an outlier among high-grade tumors, in that ADC and CBF values at presentation were more similar to LGG than HGG, although the breakdown of the findings according to DMG subtypes was not clear.[34]

Posterior Fossa Diffuse Midline Glioma, H3K27M–Mutant

In the posterior fossa, diffuse midline gliomas, H3K27M-mutant, may be located in the pons (most common), cerebellar peduncles, cerebellar vermis, and cerebellar hemispheres, with a heterogeneous imaging appearance.[59] DIPGs present with diffuse enlargement of the pons, often with partial encasement of the basilar artery, and effacement of the surrounding cisterns. No enhancement or heterogeneous enhancement is seen in pontine DIPG lesions, depending on the stage of presentation, with many lesions showing no contrast enhancement at the time of diagnosis (Fig. 3). Contrast enhancement is seen in the majority of other

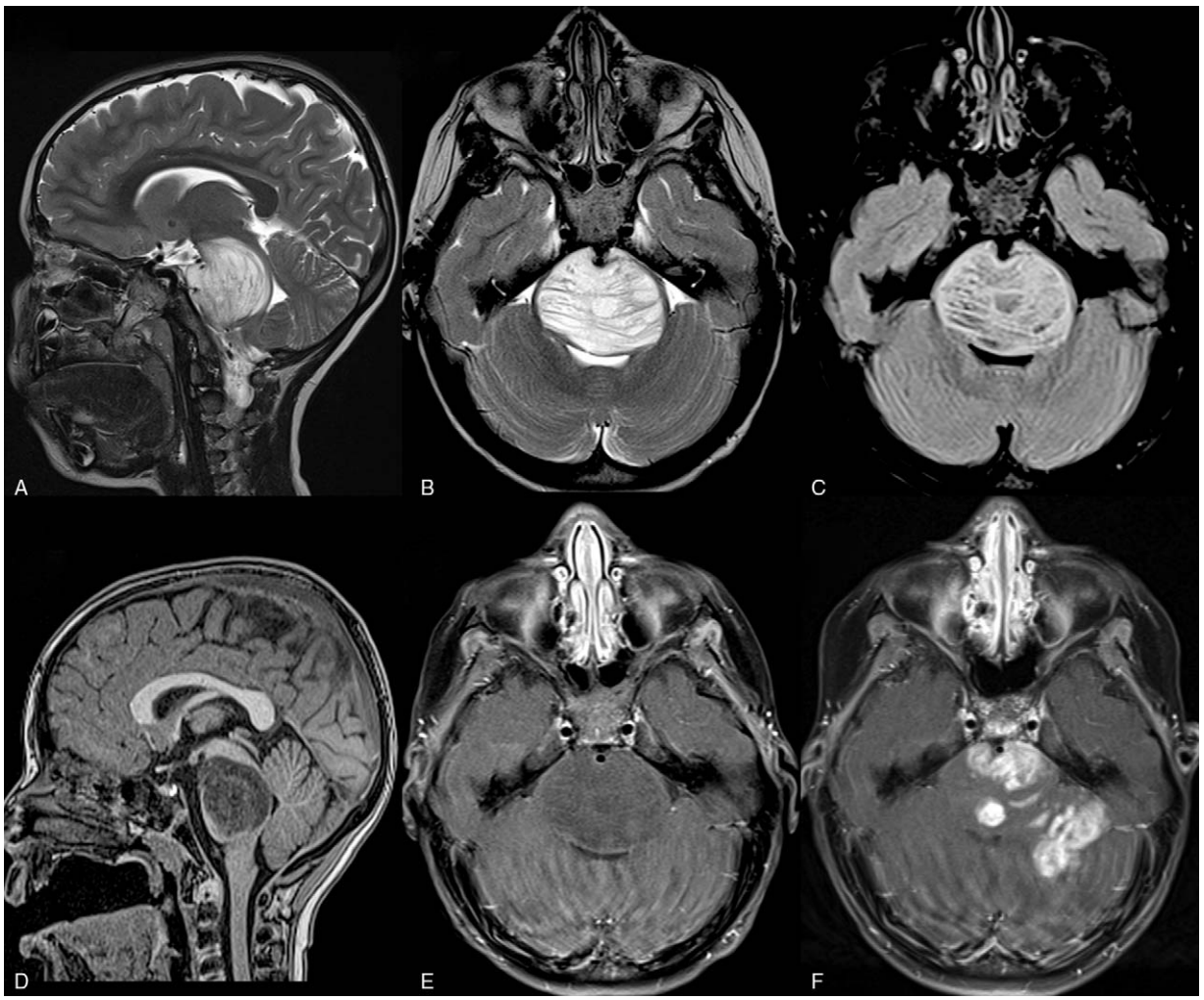

FIGURE 3. A 5-year-old patient with diffuse midline glioma, H3K27M-mutant in the pons, which had presented with headache and cranial nerve symptoms. Traditionally, these have been referred to as diffuse intrinsic pontine glioma (DIPG). A–D, Sagittal T2, axial T2, axial FLAIR, and sagittal T1 images show an expansile mass centered within and involving almost the entirety of the pons. There is partial encasement of the basilar artery. E, Axial postcontrast T1-weighted images does not show contrast enhancement in this tumor. F, Follow-up imaging at 6 months shows areas of avid contrast enhancement and extension of the neoplasm.

cases in the posterior fossa. In addition to mass effect, most of these lesions present with an infiltrative pattern, irregular borders, and cystic components or necrosis. Other less common findings include direct cortical invasion, multifocality, edema, and CSF seeding.[59] On follow-up imaging, the majority of the patients had signs of progression/recurrence and there was CSF seeding in a small proportion of those cases.[59]

Thalamic Diffuse Midline Glioma, H3K27M–Mutant

The thalamus is the second most common location of diffuse midline glioma, H3K27M–mutant. These lesions are more commonly unilateral and have variable imaging features (Fig. 4). On FLAIR, lesions typically demonstrate hyperintensity with either an apparently circumscribed or an infiltrative pattern. Necrosis is seen in around half of the patients. Variable degree of enhancement is also

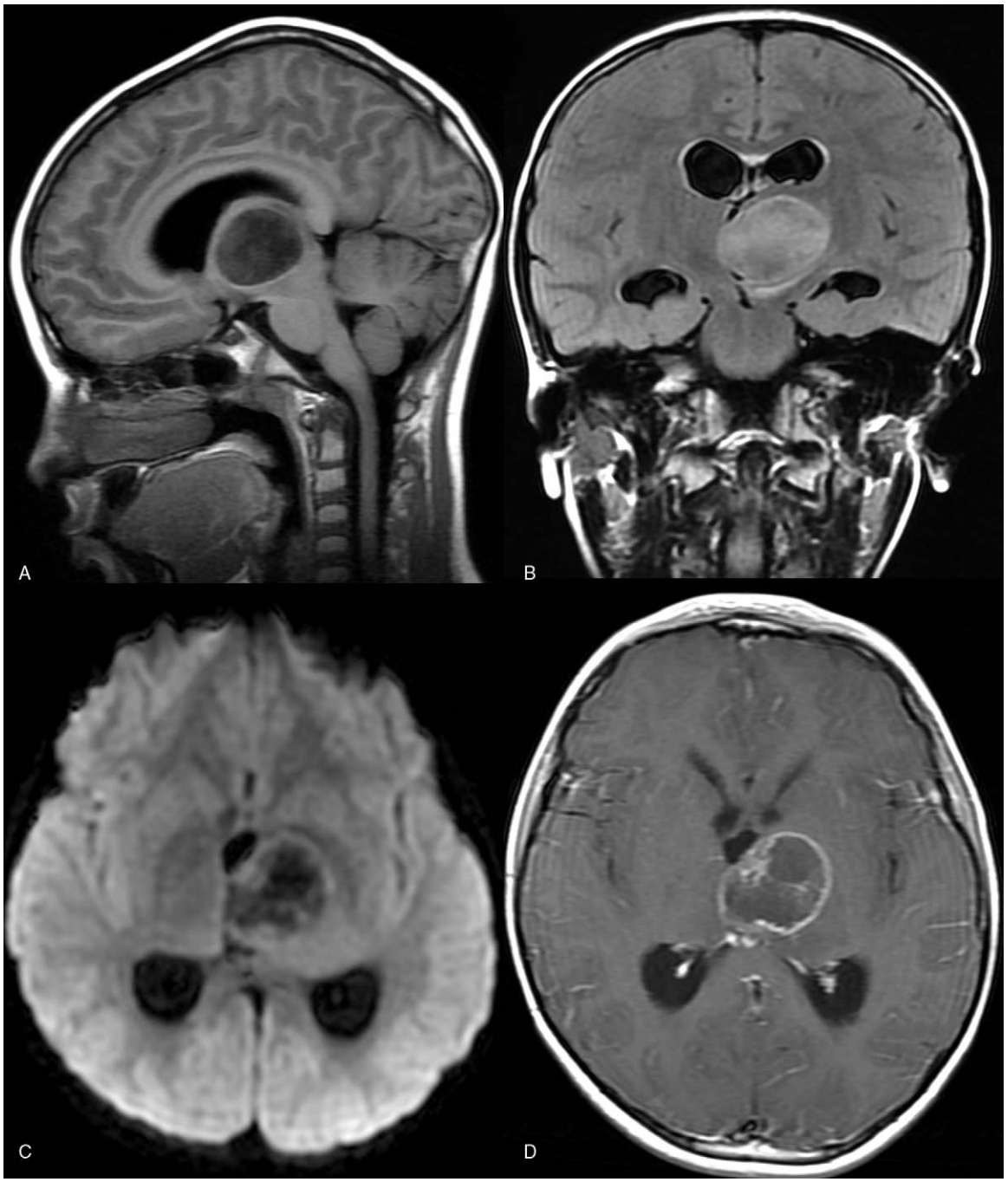

FIGURE 4. A 12-year-old patient with diffuse midline glioma of the left thalamus. Sagittal T1-weighted and coronal FLAIR (B) images a mass centered in the left thalamus bulging into the third ventricle. There is heterogeneous diffusion with mild restricted diffusion in the rim (C). Postcontrast T1-weighted images (D) show heterogeneous enhancement with a thin enhancing rim and central nonenhancement/necrosis.

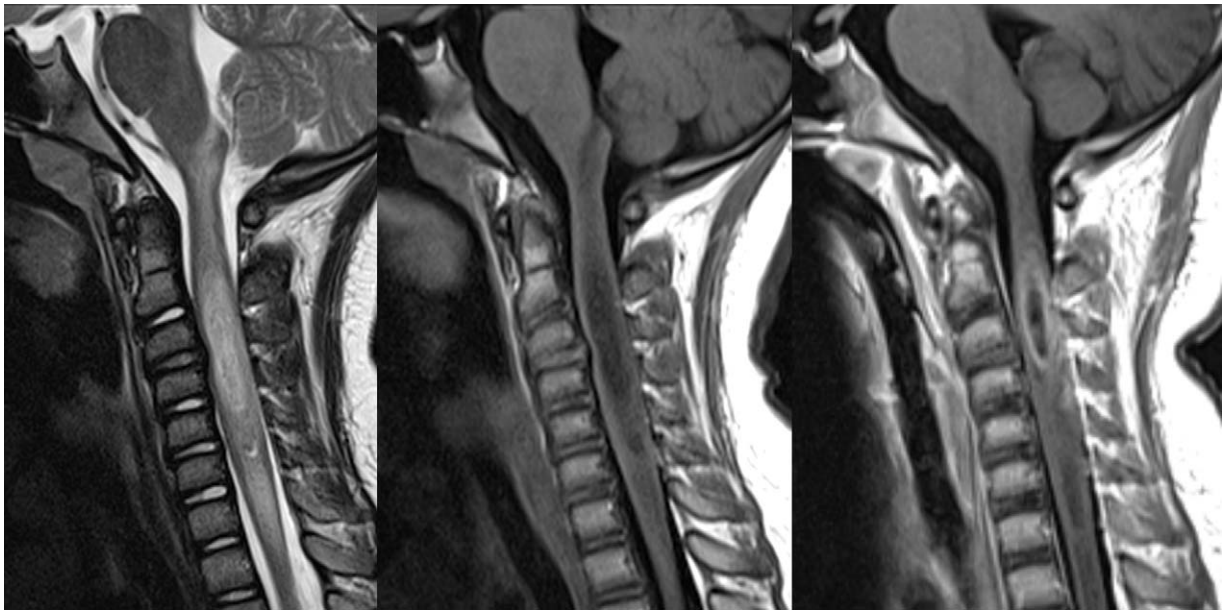

FIGURE 5. An 11-year-old female presenting with extremity weakness. Sagittal T2-weighted (A), T1-weighted (B), and postcontrast T1-weighted (C) images show a T2-hyperintense, T1-hypointense expansile lesion in the cervical spinal cord demonstrating heterogeneous contrast enhancement in some portions of the mass and central area of nonenhancement. This lesion was eventually diagnosed as a diffuse midline glioma of the spinal cord.

detected in approximately half of the patients, which can be mild or avid, or demonstrate thick rim of enhancement. Edema and multifocally are less common features. Local recurrence and distant CSF-based metastatic disease may occur.[59]

Spinal Cord Diffuse Midline Glioma, H3K27M–Mutant

Midline glioma, H3K27M–mutant is uncommonly found in the spinal cord. Lesions in the cord are typically irregular and with infiltrative borders (Fig. 5). Cord expansion, necrosis, variable enhancement, and mass effect is often seen.[59] These lesions may grow along the spinal cord to involve additional segments and have a poor prognosis.

Posttreatment Changes in Diffuse Midline Glioma

Due to the unique challenges associated with pediatric patients and peculiarities of pediatric brain tumors, a specific working group on pediatric neuro-oncology was created, the Response Assessment in Pediatric Neuro-Oncology (RAPNO).[62] According to their first publication, ''The goal of RAPNO is to propose optimal endpoints and study designs, develop a consensus on the radiological assessment for clinical trials involving children with brain tumors, and better define response so that it reflects drug activity.[62],,

Designing response assessment criteria for diffuse midline glioma is challenging mainly because of a subset of lesions that do not enhance and that tumoral size reduction does not necessarily translate into improved survival.[62] Besides, conventional MRI alone cannot reliably differentiate pseudoprogression and pseudoresponse, 2 important therapy-related issues.[62] Furthermore, there have been major changes in the brain tumor classification paradigms since the incorporation of molecular biology features. RAPNO has not delivered yet specific guidelines on the diffuse midline glioma response assessment.

Despite numerous clinical trials, chemotherapy has shown limited effect on DIPG. After initial radiotherapy, particularly proton therapy, there may be decreased size of DIPG tumors, but they inevitably progress after a variable amount of time. Pseudoprogression and new contrast enhancement may also be observed. According to Hipp et al, [63] increased DSC perfusion at any point was associated with shorter survival, and increasing perfusion over time was a poor prognostic factor in DIPG. Steffen-Smith et al [64] used spectroscopy to monitor DIPG patients and found that Cho:NAA ratio was shown to be a prognostic factor; patients with a Cho:NAA ratio higher than 2.1 demonstrated a greater risk of early mortality than those with a ratio $\leq$2.1. During follow-up, changes in this ratio had an impact on prognosis with an increase in the Cho:NAA ratio being inversely associated with survival and decreasing Cho:NAA ratio being associated with a longer life expectancy.[64]

Jansen et al[65] have developed a DIPG survival prediction tool based on multivariate analysis in 316 patients that can be used for predicting outcome and risk stratification. They report 5 prognostic variables. Age $\leq$3 years, longer symptom duration at diagnosis, and use of oral and intravenous chemotherapy were favorable predictors, whereas ring enhancement on MRI at diagnosis was an unfavorable predictor. The model could distinguish between patients with very short, average, and increased overall survival (medians of 7.0, 9.7, and 13.7 months, respectively). However, the area under the receiver operating characteristic curve obtained was 0.68.[65]

According to Castel et al, [11] patients with diffuse midline gliomas with a mutation in the H3.3 protein had worse overall survival as compared to the H3.1-mutated subgroup. Also, according to this group, the type of histone was the most important predictive factor of overall survival, and that contrast enhancement alone did not play a significant role in predicting overall survival.[11] Comparing survival rates between histone H3 wild-type and H3K27M-mutant diffuse midline gliomas, Aboian et al [36] have found that lower ADC values may correspond to a lower survival rate at 1 year after

diagnosis. Patients who survived <1 year after diagnosis had lower median ADC (1.10×10^{-3} mm^2/s; 95% CI, 0.90–1.30) than patients who survived >1 year (1.46×10^{-3} mm^2/s; 95% CI, 1.19–1.67; $P < 0.06$).

OTHER MALIGNANT PEDIATRIC GLIOMA PROFILES

Isocitrate Dehydrogenase Mutated Pediatric High-Grade Glioma

Pathogenic variants in the *IDH1* and *IDH2* genes are responsible for the vast majority of low-grade and secondary HGGs in adults. These are uncommon in the pediatric population and mostly restricted to the adolescent subgroup.[66] *IDH1/2*-mutated tumors are more commonly associated with a frontal predominance, well-defined borders, cortical involvement, less peritumoral edema, lack of enhancement, and lower choline–creatine ratios than other tumors.[67] Another important feature described as a specific imaging biomarker for the *IDH*-mutant, 1p/19q non-codeleted gliomas is the presence of T2-FLAIR mismatch (suppressed signal intensity of the tumor on FLAIR sequence in areas of high T2 signal).[68] Although this imaging finding is considered a hallmark for the *IDH*-mutant glial tumors, it is generally a feature of lower-grade gliomas and should not be necessarily be expanded to the HGGs.

H3G34-Mutated Pediatric High-Grade Glioma

Since 2012, 2 subtypes of pathogenic variants affecting the *H3F3A* gene have been described for the molecular distinction of pediatric HGGs, one resulting from an amino acid exchange in K27M (as described previously) and another leading to exchanges in G34R/G34V, which are less common.[9] The G34R/V mutations are less common in children and vary from 4.3% to 16%, with a potential geographical variability.[69] Although this mutation is more frequently observed in grade IV glioblastomas (Fig. 2), it can also be present in astroblastomas and AAs.[69]

G34R/V-mutant tumors are typically located in the cerebral hemispheres, particularly frontal and temporal lobes, tend to occur in older children with a median age of 18 years old, and with a slightly better prognosis when compared with K27M-mutated tumors. MRI of H3-G34-mutated tumors demonstrates heterogeneous signal and often with absent or mild contrast enhancement.[69] At times, the imaging appearance of these tumors may seem to not correspond to the imaging pattern of HGG.[70] A gliomatosis pattern and intratumoral calcification or hemorrhage have also been described in a few cases.[69]

Anaplastic Pleomorphic Xanthoastrocytoma

Pleomorphic xanthoastrocytoma (PXA) is an uncommon glial tumor, representing less than 1% of all glial neoplasms, most frequently occurring in children and young adults.[71] On the basis of histopathologic characteristics, the 2016 WHO update has divided PXA into two separate entities: WHO grade II PXA and WHO grade III (anaplastic PXA - APXA).[6,8] Previous studies have suggested that APXA is more likely a result of the dedifferentiation of a primary PXA than a de novo tumor.[72,73] The factors that induce anaplastic changes are mostly uncertain, although some molecular signatures have emerged.[74] These tumors are histone- and IDH1-wildtype HGGs. PXAs are genetically defined by the combination of *CDKN2A* biallelic inactivation and *RAF* modifications. Additional genetic alterations, highlighting the *TERT* amplification or promoter mutation, have shown to be a potential molecular marker of PXA associated with anaplastic progression.[74] The distinction may have therapeutic implications, as APXA is associated with a worse prognosis and may require adjuvant therapies.[75]

Imaging studies, mainly MRI, can occasionally be helpful for the differentiation of grade II PXA and APXA. Classical PXA is more frequently observed as well-defined lesions, with solid-cystic appearance presenting with superficial location and a reactive enhancing dural tail. APXA, in contrast, tends to show a more aggressive imaging presentation, mimicking other HGGs. Conventional MRI findings, such as large size lesions with heterogeneous areas of contrast enhancement, presence of peritumoral edema, lower ADC ratios, and high rCBV, are more frequently observed in APXA than PXA grade 2.[76]

Ependymoma, RELA Fusion Positive, and Anaplastic Ependymoma

The WHO classification for intracranial ependymomas (papillary, tanycytic, clear-cell, anaplastic) has been shown to have limited clinical and prognostication utility.[6,8] Since the release of the 2016 WHO Classification of Tumors of the CNS, ongoing studies are demonstrating additional data for a more satisfactory subclassification of these tumors in the future. Apart from these challenges in approaching ependymomas classification, one new entity, Ependymoma, *RELA* fusion-positive, was recently incorporated into the WHO classification.[6,8,59] This new entity accounts for the majority of supratentorial ependymomas (approximately 70%),[77] and has a worse outcome when compared with the second most frequent supratentorial ependymoma group, the *YAP1* fusion ependymomas. From an imaging perspective, *RELA*-fusion positive ependymomas are predominantly hemispheric tumors, with an extraventricular location, and often associated with cysts and necrosis.[78]

Anaplastic ependymomas (WHO grade III ependymomas) are uncommon, and in contrast to the grade II ependymomas, they have a higher incidence of CSF dissemination at the time of diagnosis and a worse outcome.[79] Similar to other subgroups of ependymoma, classical imaging features are heterogeneous tumors showing foci of calcification and hemosiderin, presenting as areas of low signal intensity on susceptibility sequences,[80] along with cystic components. Anaplastic ependymomas tend to show lower ADC values in comparison to classical ependymomas and more aggressive characteristics; nevertheless, some overlap exists, thus sometimes preventing a more constrained imaging interpretation.

PEDIATRIC HIGH-GRADE GLIOMA IN CANCER PREDISPOSITION SYNDROMES

Cancer predisposition syndromes (CPS) can be found in up to 10% of children with cancer.[81] The discovery of germline mutations leading to CPS is of importance for patients and their family members. Once discovered, continued surveillance of patients with CPS may enable early detection, which has proven to improve patient survival in some instances.[82,83]

There are numerous CPSs and a comprehensive list of conditions can be found in the references.[84–86] Neurofibromatosis type 1 (NF1) is the most common CPS in pediatrics.[81] Most NF1 tumors are benign, the most common being optic pathway glioma, which tends to arise in early childhood, affecting approximately 15% to 20% of individuals with NF1.[87] Some other CPS associated with neoplasms affecting the CNS include Noonan syndrome (dysembryoplastic neuroepithelial tumor); tuberous sclerosis (giant cell astrocytoma); familial retinoblastoma (retinoblastoma); Fanconi anemia (medulloblastoma); L-2-hydroxyglutaric aciduria (gliomas); Von Hippel-Lindau syndrome (hemangioblastoma and endolymphatic sac tumor); Turcot syndrome (ependymoma, medulloblastoma, and GBM); basal cell carcinoma syndrome (medulloblastoma); neurofibromatosis type 2 (schwannoma, meningioma, and ependymoma); Cowden syndrome (dysplastic cerebellar gangliocytoma or Lhermitte-Duclos disease); and *DICER1* mutation (pituitary blastoma, pineoblastoma).[84,88]

The CPS most commonly associated with pediatric HGGs are LFS and constitutional mismatch repair deficiency (CMMRD).[81]

Importantly, CMMRD can mimic NF1, and some current opinions suggest that in cases of high-grade tumors, including pediatric HGG, in a child with NF1, perhaps further genetic testing should be performed.[89]

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is an autosomal dominant CPS, characterized by a high frequency of malignancies in multiple organs and paucity of many other clinical features.[90] Current clinical criteria for LFS have been published elsewhere.[91–94] Germline mutation in the *TP53* gene has been identified in 70% of families meeting classic criteria for LFS, and approximately 30% meeting the more relaxed criteria for Li-Fraumeni like families.[95] The p53 protein is a transcription factor linked to conserving genomic integrity by regulating cell cycle progression and cell survival. p53 mutations are the most prevalent genetic alteration observed in human cancer.[96] The penetrance of cancer in p53 mutation carriers is high, and up to 41% of children will develop cancer by the age of 18 years.[93] CNS tumors are the second most common malignancy in children with LFS.[93] Patients with LFS have a high risk of developing astrocytoma, glioblastoma, medulloblastoma, and choroid plexus cancer. Although HGGs are the most common brain tumor in LFS, they tend to occur during late childhood and adulthood.[81] In patients with LFS, there is a potential survival advantage in patients undergoing regular tumor detection surveillance.[83]

Constitutional Mismatch Repair Deficiency

Mismatch repair (MMR) proteins remove errors from newly synthesized DNA, improving the fidelity of DNA replication. MMR protein loss increases predisposition to cancer. Biallelic MMR gene mutations lead to a syndrome with recessive inheritance, known as CMMRD.[97] CMMRD is frequently associated with café au lait spots or other hyper- or hypopigmented skin alterations, which may be confused with NF1. Other findings that can sometimes be present in CMMRD are venous anomalies, agenesis of the corpus callosum, and decreased levels of immunoglobulins.[98] As penetrance is high, reaching more than 90% at age 20, almost all patients will develop neoplasms during childhood. In this condition, mutations are so abundant that most individuals will develop multiple tumors, which may occur metachronously or synchronously. Pediatric HGGs are the most prevalent brain tumors in patients with CMMRD.[85] The presence of café au-lait spots, a positive family history of Lynch syndrome, and a sibling with childhood cancer in children and adolescents with pediatric HGG (or other malignancy) should raise the possibility of CMMRD.[81]

EPIGENETIC CLASSIFICATIONS

There have been considerable recent developments in characterizing the epigenetic and genomic profiles of pediatric HGGs, which in turn, are gradually transforming how these tumors are subgrouped.[77,99] It is anticipated that many of these subtypes will be incorporated in future official classifications of CNS tumors. As previously discussed, histone mutations causing epigenetic dysregulation have been identified in diffuse midline gliomas. These are seen in more than 90% of the diffuse midline gliomas arising in the brain stem,[11] in around 50% in the thalamus,[11] and around 60% in the spinal cord.[100] Nearly half of pediatric HGGs are characterized by histone mutations, with 2 epigenetic subtypes: the H3.3/H3.1 K27 subtype and the H3G34 subtype HGGs. A variety of other genomic aberrations are also commonly seen. Nearly one-third of patients constitute an H3/IDH wild-type subtype, which is further stratified into 3 epigenetic subgroups, pediatric GBM MYCN, pediatric GBM RTK1, and pediatric GBM RTK2. Alterations in the MAPK and phosphoinositide 3-kinase (PI3K) pathways have been identified in more than two-thirds of HGGs, ACVR1 mutations in approximately one-third of HGGs in the brain stem,[101] NTRK fusions in more than one-third of non-brainstem HGGs in infants,[102] as well as BRAFV600E, PIK3CA mutations, and PDGFRA mutations and amplifications.[15,103] Finally, mutations causing cell cycle dysregulation (p53, RB1 mutations) have been identified in a significant proportion of patients.[102]

Various epigenetic classification schemes of pediatric HGGs have been described, each with particular clinical, prognostic, and molecular features. For example, Mackay et al have analyzed and subdivided pediatric glial tumors into 3 subgroups based on DNA methylation analysis, including the G34 (WT-A), K27 (WT-B), and IDH1 (WT-C) groups.[31,32,66] Both WT-A (PXA and low-grade glioma-like tumors) and WT-C were more frequently observed in the hemispheres. Nearly one-fifth of HGGs had epigenetic profiles similar to PXA and LGGs. The PXA-like subtype was commonly associated with BRAFV600E mutation, characteristic of this tumor type. The LGG-like subtype is predominantly seen in infantile GBM patients.[15,103] These are linked to a better outcome when compared with the WT-B subjects. Although the landscape of these epigenetic descriptions is complex and continuously changing, they do provide a means for better understanding of the heterogeneous nature of pediatric gliomas and may provide targets for individualized targeted treatments in the future.

CONCLUSION

Molecular and genetic characterization of pediatric brain tumors is continuously changing how these tumors are classified. These are starting to have profound implications for brain tumor management. In our opinion, the future of brain tumor treatment choices and response assessment will rely on molecular diagnosis refinement and multiparametric imaging analysis. The combination of qualitative and quantitative MRI with molecular imaging techniques will potentiate the intrinsic limitations of contrast enhancement and tumor size assessments alone. Moreover, the inclusion of artificial intelligence tools may be useful to determine the optimal parameters and thresholds for addressing specific questions in tumor classification, prognostication, and response assessment.

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