2021 WHO classification of tumours of the central nervous system: a review for the neuroradiologist

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Abstract

The fifth edition of the World Health Organization Classification of Tumours of the Central Nervous System (WHO CNS5) published in 2021 builds on the 2016 edition and incorporates output from the Consortium to Inform Molecular and Practical Approaches to CNS Tumour Taxonomy (cIMPACT-NOW). WHO CNS5 introduces fundamental changes to brain tumour classification through the introduction of new tumour families and types, especially in the paediatric population, and a revision of diagnostic criteria for some of the existing neoplasms. Neuroradiologists are central to brain tumour diagnostics, and it is therefore essential that they become familiar with the key updates. This review aims to summarise the most relevant updates for the neuroradiologist and, where available, discuss the known radiophenotypes of various new tumour types to allow for increased accuracy of language and diagnosis. Of particular importance, WHO CNS5 places greater emphasis on organising tumours by molecular type to reflect biology, as well as to allow for better planning of treatment. The principal updates in adult tumours concern

the molecular definition of glioblastoma, restructuring of diffuse gliomas and the introduction of several new tumour types. The updates to the paediatric classification are protean, ranging from the introduction of new types to establishing separate tumour families for paediatric-type gliomas. This review summarises the most significant revisions and captures the rationale and radiological implications for the major updates.

Keywords

World Health Organization; brain tumour; central nervous system; classification; diagnosis.

Key Points

- The fifth edition of the WHO Classification of Tumours of the Central Nervous System places an increased emphasis on molecular data to reach a comprehensive integrated diagnosis.
- Several new tumour types and subtypes have been introduced, especially within the families of paediatric-type diffuse gliomas and embryonal tumours.
- Diffuse gliomas are now separated into paediatric-type and adult-type based on their underlying molecular differences.
- Diffuse paediatric gliomas are now divided into two families: paediatric-type diffuse low-grade gliomas and paediatric-type diffuse high-grade gliomas.
- Glioblastomas are adult-type tumours and are IDH-wildtype.
- Ependymomas are now classified according to a combination of histopathological and molecular features as well as anatomical location.

Introduction

Recent years have brought rapid advances in our understanding of the molecular and genetic factors that underpin central nervous system (CNS) tumour pathogenesis, behaviour, and treatment response. To incorporate this dynamic evolution of knowledge, classification systems require adaptation accordingly. The fifth edition of the World Health Organisation (WHO) Classification of Tumours of the CNS tumours (WHO CNS5) builds on the 2016 version which, for the first time, integrated molecular data into brain tumour diagnostics [1]. The latest WHO CNS5 additionally incorporates several of the key recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumour Taxonomy (cIMPACT-NOW) [2]. The key progress of the new 2021 update is a greater emphasis on molecular diagnostics in CNS tumour classification which serve to complement existing histological and immunohistochemical approaches. In addition, for the first time, WHO CNS5 separates adult-type from paediatric-type diffuse gliomas. Two new tumour families (i.e., paediatric-type diffuse high-grade glioma, paediatric-type diffuse low-grade gliomas) have therefore been added. Although these tumours present primarily in childhood, it is important to note, that some of these tumours may present in adulthood, usually in young adults. Similarly, adult-type diffuse gliomas may, less frequently, present in adolescence [current 1]. Given the central role of imaging in brain tumour diagnosis, this paper serves to update the practising neuroradiologist on the most important revisions. We have focussed on the new tumour families and types and where available, the typical radiophenotype is presented through a combination of detailed figures and a review of the up-to-date literature.

Overview of the CNS Tumour Classification

A comprehensive account of how WHO CNS5 was formulated has already been provided elsewhere [3]. For this paper, we will summarise key changes to taxonomy, nomenclature and grading. Fig. 1 gives an overview of the classification with new tumour types in grey cells.

The molecular era

WHO CNS5 places greater emphasis on molecular classification given the significant advances in knowledge regarding the molecular basis of CNS tumours. This refines the grouping of CNS neoplasms, ultimately to further define prognosis and treatment stratification. Genes and proteins that are clinically and pathologically relevant to the latest classification and new tumour groups will be highlighted throughout this paper. The increased emphasis on molecular profiling in WHO CNS5 is delivered through an expanding use of advanced pathological techniques. Of particular relevance to the new classification is methylation profiling, which represents an important adjunct for tumour diagnostics [4-7].

The overarching goal of the WHO CNS5 classification is a high reproducibility in the classification of CNS tumours. This may be reached through a variable combination of histological and molecular techniques. For this reason, WHO CNS 5 is proposed as a 'hybrid taxonomy' which likely represents an intermediate stage towards increasingly accurate future classifications.

Standardizing nomenclature and grading

In WHO CNS5, the term tumour 'type' replaces 'entity', and the term 'subtype' is used instead of 'variant'. Tumours are classified within categories (e.g., embryonal tumours), families (e.g., medulloblastoma) and types (e.g., medulloblastoma, SHH-activated and *TP53*-wildtype). In addition, subtypes and subgroups may be recognized (e.g., four provisional subgroups of SHH-activated medulloblastoma). Moreover, WHO CNS5 strictly follows the HUGO Gene Nomenclature Committee (HGNC) system for gene symbols and the Human Genome Variation Society (HGVS) recommendations for sequence variants [8, 9]. CNS tumour grading now conforms with grading in non-CNS tumours, with grading applied within tumour types as opposed to across different tumour types [3]. To help distinguish it from the previous classification Arabic numerals (i.e., CNS WHO grade 1-4) have replaced Roman numerals in the grading system.

Integrated layered diagnosis

In parallel with advancing knowledge, molecular and histopathological parameters are presented in a layered report with an integrated diagnosis reached through a combination of these features. The new classification retains the use of this layered report structure for the documentation of tumour type as endorsed previously by the International Society of Neuropathology-Haarlem

consensus guidelines and the International Collaboration on Cancer Reporting [10, 11]. To maximize classification accuracy and provide increased diagnostic clarity, WHO CNS5 has established ‘essential’ and ‘desirable’ criteria for each tumour type that specifies which combinations of diagnostic criteria are sufficient for a conclusive integrated diagnosis to be reached. If this is not possible, the terms “not otherwise specified” (NOS, in case necessary information to make the diagnosis is not available) and “not elsewhere classified” (NEC, diagnostic testing performed was not conclusive) may be used.

Specific changes

Changes to specific categories and families of tumours will be the focus of the remainder of this manuscript. These can be broadly divided into two categories: newly recognized tumour types and known tumour types with revised nomenclature, placement within families or changes to WHO grading [3]. For some newly defined tumour types characteristic imaging features have been recognized and will be described.

Gliomas, glioneuronal tumours and neuronal tumours

These tumours are now categorized into six different families: Adult-type diffuse gliomas, Paediatric-type diffuse high-grade gliomas, Paediatric-type diffuse low-grade gliomas, Circumscribed astrocytic gliomas, Glioneuronal and neuronal tumours and Ependymal tumours. These tumour families include 14 newly recognized types. For the first time, a distinction is made between diffuse gliomas occurring mostly in adults versus those occurring primarily in children. This distinction reflects growing evidence for the molecular differences between paediatric-type diffuse astrocytic tumours and those arising in adults.

Adult-type diffuse gliomas

Previously, 15 entities were described under this category in 2016. These have now been reduced to three types according to genetic details and corresponding prognostic differences: *(1) Astrocytoma, IDH-mutant, (2) Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, and (3) Glioblastoma, IDH-wildtype* (Fig. 2). Among the reasons behind this simplification is an

increased understanding of specific tumour biology and an increased utilisation of molecular diagnostics [12].

1. *Astrocytoma, IDH-mutant (CNS WHO grade 2, 3 or 4)*, may be diagnosed if *IDH1*- or *IDH2*-mutations are present in a diffuse glioma and there is ATRX loss/mutation or absence of 1p19q codeletion. Additional desirable criteria include *TP53* mutation, methylation profile of astrocytoma, IDH-mutant and astrocytic differentiation [1]. In the previous classification, three different IDH-mutant diffuse astrocytic tumours were entered: diffuse astrocytoma, anaplastic astrocytoma and glioblastoma. In WHO CNS5, however, all IDH-mutant diffuse astrocytic tumours are considered a single type with further grading defined within that type. The grading remains mostly histological, but notably, a homozygous deletion of *CDKN2A* and/or *CDKN2B* is associated with a poor prognosis in this tumour type and its presence results in CNS WHO grade 4, regardless of other morphological features [12, 13]. It should be noted, the term IDH-mutant glioblastoma has been discontinued.

   Imaging: The imaging features of this tumour type can vary. T2-weighted imaging (T2w)–fluid-attenuated inversion recovery (FLAIR)–mismatch (Fig. 3) has been suggested as highly specific imaging biomarker for such IDH-mutant, 1p/19q non-codeleted gliomas [14]. T2-FLAIR mismatch refers to the high signal seen on T2w sequences with comparatively hypointense signal seen on FLAIR in these tumours; often with a persisting FLAIR hyperintense rim. Contrast enhancement is uncommon in WHO CNS grade 2 IDH-mutant astrocytomas but is seen at increasing frequency in the higher-grade lesions (Fig. 3) [15-17]. Perilesional signal abnormality is more typically seen around higher-grade lesions.

2. *Oligodendroglioma, IDH-mutant and 1p/19q-codeleted*, is a diffusely infiltrating tumour and can be assigned CNS WHO grade 2 or 3. The most common presenting clinical symptom within this cohort is seizures, making up two-thirds of all presentations [18]. This tumour demonstrates a frontal lobe predilection (approximately 60% of cases) with the temporal and parietal lobes being the next most frequent locations [19, 20]. The posterior fossa and basal ganglia are uncommon locations for oligodendroglioma.

Imaging: Oligodendrogliomas are typically seen in the cortex or subcortical white matter (Fig. 4), with some showing calcification on CT [21]. On magnetic resonance imaging (MRI), variably heterogenous T2w hyperintensity with poorly defined margins is common. Contrast enhancement is present in less than a quarter of CNS WHO grade 2 tumours but greater than 70% of grade 3 lesions, where it is associated with a poorer prognosis [22-24]. Oligodendrogliomas can show higher relative cerebral blood volume (rCBV) and lower apparent diffusion coefficient (ADC) values when compared to IDH-mutant diffuse astrocytomas of a similar grade, thereby mimicking more aggressive disease [25].

3. *Glioblastoma* (GBM) is the most common malignant brain tumour occurring in adults, accounting for up to half of all primary malignant tumours [26]. Numerous recent studies have demonstrated that astrocytic tumours, which do not fulfil the light microscopic criteria for CNS WHO grade 4 (i.e., microvascular proliferation and necrosis) but share typical molecular aberrations of GBM exhibit, in most cases, a similarly malignant clinical course [27-29]. Therefore, the presence of *TERT* promoter mutation, *EGFR* gene amplification or +7/−10 chromosome copy-number changes are considered glioblastoma-defining in the context diffuse IDH-wildtype H3-wildtype astrocytomas [30, 31]. As a result, IDH-wildtype H3-wildtype diffuse astrocytic tumours with the aforementioned genetic features of glioblastoma are now assigned the highest CNS WHO grade regardless of histology [32, 33].

   Imaging: This is relevant for the neuroradiologist, because molecularly-defined glioblastomas may lack necrosis or parenchymal enhancement on MRI (Fig. 5, A-C) [34].

Paediatric-type high-grade diffuse gliomas

As mentioned above, paediatric-type diffuse gliomas are now separated from adult-type diffuse gliomas in recognition of the clinical and molecular distinctions between these groups. Under the new classification, glioblastoma is no longer a tumour type in the paediatric-type high-grade glioma family, but it recognises four different types: (1) *Diffuse midline glioma, H3 K27-altered,* (2) *Diffuse hemispheric glioma, H3 G34-mutant,* (3) *Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype*, and (4) *Infant-type hemispheric glioma.*

1. *Diffuse midline glioma (DMG), H3 K27-altered* is an infiltrative midline glioma with the name now expanded to include different mechanism for the loss of H3K27 trimethylation other than just H3K27 mutations (e.g., EZH inhibitory protein (EZHIP) overexpression) [35]. These tumours are typically located in the brainstem or pons but can be located in the thalamus (where they can be bithalamic) or occur elsewhere along the cerebral midline or spinal cord [36, 37]. It has been shown that bilateral thalamic tumours are more frequent in the *EGFR*-mutant subtype [35, 38, 39].

   Imaging: In the brainstem, imaging features are those of the previous WHO entity of diffuse intrinsic pontine glioma (DIPG). Imaging has been described elsewhere [45], [46], [47]. T2w hyperintensity is typical, however T2/FLAIR signal and enhancement patterns are variable, with some lesions showing no enhancement [39]. Chen *et al.* have proposed that ADC values can be used to non-invasively predict the H3 K27M mutational status in diffuse midline gliomas. Specifically, minimal ADC and peri-tumoural ADC values were significantly lower in H3 K27M-mutant gliomas compared with H3 K27M -wildtype gliomas [40, 41], however variability of ADC has been highlighted by another study [42]. Occurrence in other sites, such as hypothalamus, pineal region or cerebellum have rarely been reported [43, 44]. Bithalamic gliomas (Fig. 6), especially those that are *EGFR*-mutated appear to have a particular dismal prognosis with median survival times between 10-14 months [39].

2. *Diffuse hemispheric glioma, H3 G34-mutant* is a neoplasm of the cerebral hemispheres (CNS WHO grade 4), occasionally extending to midline structures. H3 G34-mutant gliomas represent less than 1% of all gliomas but 15% of high-grade gliomas in adolescents and young adults [48]. Cases of leptomeningeal spread have been reported [49].

   Imaging: The MRI features of these tumours are similar to other high-grade gliomas, typically showing an enhancing tumour with mass effect. Internal areas of necrosis, haemorrhage, and calcification have been reported although no pathognomonic features are known [50]. Tumours may present as multi-focal lesion (Fig. 7). It should be noted that, like other ‘paediatric-type’ gliomas, diffuse hemispheric glioma also occurs in the adult population, and in fact has a median age of 18 years at diagnosis [51]. In the adult cohort described by *Picart et al.* (range: 19-33 years), all tumours were monocentric. Midline

involvement was evident in 4 cases but always as an extension of the primarily hemispheric tumour. Most patients demonstrated either no or faint enhancement, were cortical or subcortical in location, poorly delineated, infiltrative lesions mostly in a frontoparietal location [51]. All but one H3 G34R-mutant glioma showed areas of restricted diffusion (Fig. 7), and half of the tumours studied showed increased perfusion.

3. *Diffuse paediatric-type high-grade glioma (pHGG), H3-wildtype and IDH-wildtype* is a CNS WHO grade 4 malignancy with aggressive glioblastoma-like histological features (mitotic activity, vascular proliferation or necrosis) or a primitive, undifferentiated morphology [1]. The terms glioblastoma or paediatric glioblastoma are not recommended. These tumours have been reported to occur throughout the supratentorial brain, brainstem and cerebellum [52].

   Imaging: Imaging features include poorly marginated heterogenous lesions most commonly in the cerebral hemisphere. Lesions are typically hyperintense on FLAIR with thick, irregular rim enhancement and restricted diffusion in the solid components [53]. Diffuse paediatric-type high-grade glioma MYCN is a recognised subtype which has been described to occur in the supratentorial brain in the majority (86%) of cases [52]. It has been suggested that the pHGG MYCN subtype may well be a more circumscribed lesion, with only minimal perilesional signal abnormality and homogenous contrast enhancement [54, 55]. Specific imaging characteristics for the other subtypes; RTK1 and RTK2, have not been reported yet.

4. *Infant-type hemispheric glioma* was introduced as a new type and is a cerebral hemispheric, high-grade cellular astrocytoma, typically associated with receptor tyrosine kinase fusions in the NTRK family, *ROS1*, *ALK* or *MET* [56-58]. All reported cases have been in early childhood with a median age at presentation of 2.8 months in one cohort [59]. Clinically, these lesions can present acutely with non-specific symptoms such as lethargy and increased head circumference. These tumours occur supratentorially, usually as large masses that can demonstrate superficial involvement including leptomeningeal extension [57].

Imaging: From the limited imaging reports published, the tumours presented with solid and large internal cystic components and areas of intratumoural haemorrhage (Fig. 4) [59-61]. Occasional cases have shown leptomeningeal dissemination, therefore spinal MRI is recommended [62]. The total number of cases within each molecular subtype (NTRK-altered, *ROS1*-altered, *ALK*-altered and *MET*-altered) remains extremely small precluding further description here. Fig. 8 shows an example of an infant-type hemispheric glioma with TRIM24-MET fusion.

Paediatric-type low-grade diffuse gliomas

Overall, paediatric low-grade gliomas are the most frequent brain tumours in children accounting for approximately 30% of all cases with circumscribed gliomas (discussed below) being far more common than diffuse low-grade gliomas [63, 64]. The need to separate adult and paediatric diffuse low-grade gliomas is evident given the differing genetic landscape and the more aggressive clinical course of low-grade gliomas in adults, where they have a higher propensity for malignant transformation [65]. The category of paediatric-type diffuse low-grade glioma was introduced to distinguish tumours driven by an activation in the mitogen-activated protein kinase (MAPK) pathway from adult-type low-grade gliomas which are usually IDH-driven [66]. The new tumour types introduced in this family are *(1) Diffuse astrocytoma, MYB- or MYBL1-altered, (2) Polymorphous low-grade neuroepithelial tumour of the young (PLNTY) and (3) Diffuse low-grade glioma, MAPK pathway-altered. (4) Angiocentric glioma* was previously listed under 'Other gliomas' in the WHO 2016 classification.

1. *Diffuse astrocytoma, MYB- or MYBL1-altered* is a rare (2% of all paediatric low-grade gliomas) infiltrative neoplasm designated a CNS WHO grade 1 [66]. The largest series to date reported on twenty patients with a median age of 29 years [67]. Paediatric studies so far included less than 11 patients [68-70]. This tumour is typically supratentorial in location with cortical and subcortical involvement and has been most commonly reported in the temporal lobe (42.5% of cases) followed by frontal and occipital locations [71, 72]. Children with this tumour typically present with drug-resistant epilepsy with the median age of onset of 10 years [67, 73].

Imaging: Imaging descriptions are of hyperintensity or mixed signal intensity on FLAIR without (or minimal) enhancement or diffusion restriction (Fig. 9). Focal and diffuse growth patterns have been observed (Fig. 9), and large cysts have been reported [74, 75]. Limited data suggest a relatively benign course with 9 of 11 children stable or even showing disease resolution over a 12-year follow-up [74]. For those presenting with drug-resistant epilepsy, surgery appears effective with 90% becoming seizure-free following resection [67].

2. In 2017, Huse *et al.* described a molecularly distinct epileptogenic neoplasm termed *Polymorphous low-grade neuroepithelial tumour of the young (PLNTY)* which may account for a proportion of oligodendroglioma-like tumours in the paediatric population [76]. This lesion tends to present during teenage years, often with refractory epilepsy. Histologically, the lesion demonstrates both infiltrative and compact growth patterns with oligodendroglioma-like components with coarse calcification in the majority of cases. The tumour often carries genetic changes in the MAPK pathway e.g., *BRAF* mutations or FGFR (particularly *FGFR2* or *FGFR3*) fusions [76]. PLNTY is found in the temporal lobe most often (80% of cases), more so on the right than left [77, 78].
   Imaging: Characteristic imaging appearances include a cortical/subcortical location in the temporal lobe, with calcification and cysts in the majority of cases [77]. PLNTY tend to be T2w hyperintense lesions with little or no contrast enhancement. A granular appearing calcification pattern termed ‘salt and pepper sign’ on T2w sequences has been proposed as a potential manifestation of this type [78]. The key radiological differential for PLNTYs is a dysembryoplastic neuroepithelial tumour (DNET), which show calcification less frequently and are more likely to demonstrate a FLAIR hyperintense rim. It has been proposed that PLNTYs are generally smaller and DNETs tend to be more clearly demarcated and multinodular, displaying the so-called ‘soap bubble sign’ [78, 79].

3. *Diffuse low-grade glioma, MAPK pathway-altered* are tumours that have an astrocytic or oligodendroglial origin and have modifications in genes encoding for MAPK pathway proteins. The three currently recognised subtypes are *FGFR1 tyrosine kinase domain-duplicated, FGFR1-mutant* and *BRAF p.V600E-mutant* [1]. These tumours are IDH- and

H3- wildtype without homozygous deletion of *CDKN2A* [80]. They typically occur in the paediatric population and epilepsy is a recognised clinical presentation. The underlying mutation is likely to have an impact on outcome. For example, Bag et al. showed that diffuse low-grade glioma, *FGFR1* TKD-duplicated has a better outcome compared with diffuse low-grade glioma *FGFR1*-mutant with 5-year progression free survival rates of 69% and 53%, respectively [65]. Currently, it is not known to which extent this group will be categorised into further discrete tumour types and prognostic factors related to the group will most likely elucidated as the molecular classification of this group is further studied. Imaging: Given the rarity, newly described nature and paucity of literature, the imaging features are also still to be revealed.

4. *Angiocentric glioma (AG)* is a diffuse glioma with nearly all cases exhibiting a *MYB-QKI* gene fusion and the remainder other *MYB* alteration [81]. AG is a rare tumour that typically arises in a cortical/juxtacortical location, most often in the frontal or temporal lobes, however thalamic and increasingly brainstem locations are recognised [82-85]. The tumour type was first described in two case reports in 2005 and most often presents in children and adolescents with drug-resistant epilepsy [86, 87]. AG is typically a focal tumour with infiltrative margins composed of bipolar glial cells orientated around a cortical blood vessel [88].

   Imaging: The tumours are hyperintense on T2w/FLAIR and non-enhancing with a rim-like T1 hyperintensity surrounding the tumour occasionally reported. Stalk-like components extending towards the lateral ventricle (Fig. 10) and calcification have also been noted although the latter is not characteristic [87, 89, 90]. On MR spectroscopy the tumour can demonstrate elevated myo-inositol and glycine, elevated choline and decreased NAA [91]. AGs generally show stability on radiological surveillance and in the majority of cases total resection is curative [90, 92].

Circumscribed astrocytic gliomas

The new type in this family is *(1) High-grade astrocytoma with piloid features*. A revised type within this family is *(2) Astroblastoma, MN1-altered* (addition of genetic details and reclassified into this family - previously listed under 'other gliomas'). Pilocytic astrocytoma was previously

listed under ‘Other astrocytic tumours’ in the WHO 2016 classification and is the most common type in this family.

1. *High-grade astrocytoma with piloid features (HGAP)* will be one of the first tumours to be defined by a specific methylation profile and was initially referred to as methylation-class anaplastic astrocytoma with piloid features (MC-AAP)[2]. HGAP has typically been described in the adult population with a median patient age of 40 years (4-88y) [1]. This astrocytoma may show a mixture of histological features including those of a high-grade astrocytoma/glioblastoma and pilocytic-like features. Alterations of the MAPK pathway are frequently combined with homozygous deletion in *CDKN2A*, *CDKN2B* and/or *ATRX* mutations. A collection of HGAPs was published by Reinhardt *et al.* in 2018 following a DNA methylation assessment of histologically defined anaplastic PAs with the median age in that cohort actually being 41.5 years [93]. Given that this is a newly recognised type, its radiological features and clinical characteristics are still emerging. HGAP most commonly arises in the posterior fossa with the cerebellum being the most common site (74%). Retrospective studies show a poor prognosis marginally better than IDH-wildtype GBMs and comparable to that of IDH-mutant astrocytoma [93]. Recently, a reanalysis of cerebellar GBMs by methylation array revealed a moderately high proportion of HGAPs (25 of 86 patients) [94]. More data are required to confirm a CNS WHO grade but current evidence suggests a clinical behaviour similar to grade 3 [1].

   Imaging: A single centre experience of 6 cases described a tendency for rim enhancement with lack of central enhancement and a generally hyperintense appearance on T2w [95]. Interestingly, diffusion restriction and cyst formation did not appear to be features in this small initial cohort. They suggested that O-(2-[^{18}F]fluoroethyl)-l-tyrosine positron emission tomography might be a useful tool for this tumour type. Within the paediatric population, descriptions are even more limited [96]. Nevertheless, they described a single case of HGAP in an eight-year-old girl with a parietal tumour who underwent resection followed by chemoradiotherapy and had an overall survival of 37 months [96]. Like PA, there does appear to be an association between HGAP and Neurofibromatosis type 1 [93, 97].

2. *Astroblastoma, MN-1 altered (AB)* is a circumscribed, glial tumour with a perivascular growth pattern and the histological hallmark of an astroblastic pseudorosette [98]. An alteration of the *MN1* gene on chromosome 22 is listed in the essential diagnostic criteria in combination with the presence of astroblastic perivascular pseudorosettes [1]. In 2016, *Sturm et al.* showed that the majority of tumours in their cohort diagnosed histologically as AB showed structural rearrangement at the *MN1* gene [99]. The tumour predominantly occurs in the cerebral hemispheres, most frequently in the frontal and parietal lobes and shows a strong female predominance (39/41 cases in one meta-analysis) [100].
   Imaging: The tumour is generally a well-demarcated, superficially located supratentorial lesion with both solid and cystic components that is hyperintense on T2w often with multiple areas of susceptibility artefact and little to no surrounding oedema [101]. AB tend to show restricted diffusion within the solid components and heterogenous enhancement characteristics. Outcome data for patients with *MN1*-altered AB are scarce but the suggest frequent local recurrence but good overall survival. Survival rates at 5 years have been reported in the region of 90% and 50% at 10 years [102].

Glioneuronal and neuronal tumours

All tumours with a neuronal component have remained grouped together in WHO CNS5 with the addition of two new types: *(1) Multinodular and vacuolating neuronal tumour (MVNT) and (2) Myxoid glioneuronal tumour* [114]. *(3) Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC)* has been included as a provisional tumour type. *(4) Diffuse leptomeningeal glioneuronal tumour*, a provisional tumour type in 2016, has now been accepted as a tumour type.

1. *Multinodular vacuolating neuronal tumour of the cerebrum (MVNT)* was first described in 2013 in case series of 10 patients with a mean age of 46 [115]. MVNT manifest as neuroepithelial cells with stromal vacuolation in a nodular formation within the deep cortex and adjacent white matter and is a CNS WHO grade 1 lesion [116-118].
   Imaging: Radiologically, it is comprised of multiple discrete round/ovoid nodules, ranging from 1-5 mm in diameter distributed along the subcortical ribbon (Fig. 11). These small nodules are hyperintense on T2w and generally do not supress on FLAIR. The lesion shows

no restricted diffusion or blooming artefact with a clear margin to adjacent tissues [119]. Described at 3T field strength, Lecler *et al.* proposed that a focus of central FLAIR suppression within the vacuolated areas can increase diagnostic confidence [120]. MVNT is supratentorial in location on the inner surface of otherwise normal cortex [121]. Clinical descriptions are of non-focal headache and/or seizure activity, although most MVNT are detected incidentally on imaging. Given the benign nature of this lesion it has been suggested to be a 'do-not-touch' lesion with typical radiological appearances precluding the need for biopsy [121, 122].

2. *Myxoid glioneuronal tumour* is a recently described neoplasm with a stereotypical location along the septum pellucidum characterised by *PDGFRA* gene mutation [123]. These are CNS WHO grade 1 glioneuronal tumours composed of oligodendrocyte-like cells in a myxoid stroma reminiscent of DNET and can present across a wide age range in children and adults, representing up to 2% of all CNS tumours [2]. Headache is the most common clinical presentation although seizures, behavioural changes and visual symptoms have been reported [124].

   Imaging: Recent case series based on the molecular diagnosis such as that by Lucas *et al.* give the clearest descriptions of this type: In this series of eight patients, tumours were located in the septum pellucidum (4/8), genu/rostrum of the corpus callosum (3/8) or in the immediate periventricular white matter (1/8) [123]. All lesions were T2w hyperintense, lacking contrast enhancement and diffusion restriction. FLAIR has been highlighted as diagnostic if it shows partially suppressed signal at the centre of the lesion resembling a T2-FLAIR mismatch as previously described in septal DNETs [125]. Tumours centred in the septal nuclei and septum pellucidum can be associated with obstructive hydrocephalus and a subset of patients have presented with intraventricular disseminated disease at the time of presentation [123, 125]. The majority were cured through surgical excision with only a minority needing further treatment [126].

3. In 2020, Deng *et al.* described a novel, methylation-defined tumour type termed, *Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters (DGONC)* [114]. The two cases series published to date show that these tumours are predominantly

seen in paediatric patients, with a median age of 9 years (range 1-75 years). All have been in a supratentorial location perhaps preferentially emerging from the temporal lobe (11/21 cases). Given the recent description of this type, clinicoradiological details are still emerging and DGONC is listed as a provisional new type in WHO CNS5 pending further published studies before full acceptance.

Imaging: A recent case series described well defined cortical or subcortical supratentorial masses that were hyperintense on T2w/FLAIR with little or no contrast enhancement (Fig. 12). Internal calcification and low ADC values centrally were also observed [127]. The five-year survival rate in the studied cases is documented at 89%.

4. *Diffuse leptomeningeal glioneuronal tumour (DLGNT)* provisionally included in the WHO 2016 update has been confirmed and included into the WHO CNS5 classification. The tumour is a molecularly defined type with MAPK pathway alteration being listed as essential diagnostic criterium. This is important as the tumour can present as a discrete parenchymal mass. Therefore, diffuse or leptomeningeal growth are not necessarily present on imaging. This neoplasm was previously referred to by multiple names including disseminated oligodendroglial-like leptomeningeal tumour, meningeal gliomatosis and diffuse leptomeningeal oligodendrogliomatosis which are discontinued [128]. The tumour has mostly been observed in children with a median age of 5 years and slight male predilection [129].

   Imaging: DLGNT preferentially involve the leptomeninges of the brain (basal cisterns) and spinal cord (Fig. 13). Nodular T2w hyperintense lesions located along the subpial surface of the brain and spinal cord may be present [130]. In the largest cohort to date (31 patients), discrete intraparenchymal lesions were found in 81% of cases, most commonly in the cord [131]. The neuroradiologist needs to be aware of this type given the similar radiological appearances to CNS infection or leptomeningeal carcinomatosis. In fact, DLGNT has occasionally been misdiagnosed as tuberculosis when presenting intracranially [132].

Ependymal tumours

Ependymomas account for approximately 10% of paediatric gliomas and up to 50% of CNS tumours under the age of 5 years [133, 134]. This family of tumours has undergone significant

restructuring since 2016, now being classified according to a combination of histological and molecular features as well as anatomical location (supratentorial, posterior fossa, spine) [135, 136]. The new types are *(1) Supratentorial ependymoma, ZFTA fusion–positive, (2) Supratentorial ependymoma, YAP1 fusion–positive, (3) Posterior fossa group A (PFA) ependymoma, (4) Posterior fossa group B (PFB) ependymoma, and (5) Spinal ependymoma, MYCN–amplified.* Known tumour types are *(6) Myxopapillary ependymoma* with changes to tumour grade and subependymoma. One molecular group at each anatomical site consists of tumours with morphological features of subependymoma. Given the limitations of ependymoma histological grading, assigning a CNS WHO grade is no longer essential as part of the diagnosis of ependymomas in the paediatric population, however, tumours are usually CNS WHO grade 2 or 3 [137].

1. *Supratentorial ependymoma, ZFTA fusion-positive* is a circumscribed glioma, can occur in adults and children and accounts for approximately 75% of supratentorial ependymomas in children [138, 139]. Fusion of the *ZFTA* gene with partner genes, mainly *RELA* is suspected to be the primary oncogenic event.

   Imaging: Tumours tend to be heterogenous hemispheric masses with cysts and necrosis with perilesional oedema (Fig. 14) [140]. Heterogenous enhancement and restricted diffusion within the solid components are typical [141, 142]. *ZFTA* fusion-positive show poorer survival outcomes compared to YAP1 fusion-positive supratentorial ependymomas [143]. Homozygous deletion of *CDKN2A/B* has been identified as an independent poor prognostic indicator [144].

2. *Supratentorial ependymoma, YAP1 fusion-positive* are located within or adjacent to the lateral ventricle and are often large at the time of presentation. These tumours are relatively uncommon, only described in the paediatric setting thus far and accounting for approximately 7% of all supratentorial ependymomas [136, 145]. A female predilection has been observed.

   Imaging: Tumours are typically isointense to cortex on T2w sequences with well-defined edges and a combination of cystic and multinodular components, with heterogenous enhancement of the solid components and variable perilesional oedema [145]. Despite

lesion size, their prognosis appears better compared to other supratentorial ependymomas with specific clinical prognostic markers still to be elucidated [146].

3. *PFA ependymomas* (Fig. 15) usually occur in infants and young children with a median age of presentation of 3 years and account for over 95% of posterior fossa ependymomas in children under six years of age, decreasing to 50% in the adolescent population [147, 148]. PFA ependymomas are more likely to arise from the roof or lateral portions of the 4th ventricle as opposed to the floor [147, 148]. This is important given that previous studies have demonstrated lower survival rates and challenges achieving a total surgical resection in laterally positioned tumours [149, 150]. Overall outcome is related to the extent of surgical excision, however PFA ependymomas are associated with a poorer prognosis compared to the PFB group [151, 152].
   Imaging: Please, see PFB ependymomas below.

4. *PFB ependymomas* mostly arise in adolescents and young adults, with a median age at presentation of 30 years.
   Imaging: Although they can occur throughout the 4th ventricle, tumours appear to arise more frequently from the ventricular floor [147]. *Yonezawa et al.* (n=16) observed imaging differences between PFA and PFB tumours. Specifically, calcification was mainly seen in PFA ependymomas whereas cyst formation was seen in PFB ependymomas. They also observed that PFB ependymomas show greater contrast enhancement rates compared to PFA ependymomas. There was no difference between the two groups in the likelihood of the lesions to advance beyond the confines of the 4th ventricle [153].

5. *Spinal ependymoma, MYCN-amplified* is a well-demarcated tumour, often (78% of cases) in the cervical or thoracic cord and most demonstrate high-grade histopathological features [154]. This represents a rare type with less than 30 cases reported in the literature (median age of presentation 31 years with a female predilection) [154, 155].
   Imaging:These tumours tend to be large with cord infiltration spanning multiple vertebral levels. Primarily intramedullary and nodular extramedullary presentations have been reported, and diffuse leptomeningeal disease is typical [155, 156]. This tumour is

aggressive with all reported patients suffering disease recurrence at follow-up despite intensive treatment [154].

6. *Myxopapillary ependymomas*, the most common tumours of the conus medullaris and filum terminale, are now considered a CNS WHO grade 2 rather than grade 1. Of note, paediatric patients are at increased risk of dissemination at the time of diagnosis, which is evident in over 50% of cases at the time of diagnosis [157, 158].

Choroid plexus tumours

Choroid plexus tumours have been separated from neuroepithelial tumours and are a distinct category. The tumour nomenclature in this group remains unchanged (i.e., choroid plexus papilloma, atypical choroid plexus papilloma and choroid plexus carcinoma).

Embryonal tumours

Medulloblastoma

Medulloblastomas (MB) are the most common embryonal brain tumours making up 20% of all childhood tumours [161]. MBs are now classified according to a combination of molecular and histopathological features and all types are CNS WHO grade 4 lesions. The molecularly defined groups in WHO CNS5 are: *(1) MB, WNT-activated, (2) MB, SHH-activated, TP53-wildtype, (3) MB, SHH-activated, TP53-mutant, and (4) MB, non-WNT/non-SHH (i.e., group 3 and 4)* [162]. Histological subtypes listed in the 2016 classification, comprising four separate groups (classic, desmoplastic/nodular, MB with extensive nodularity and large cell) have been condensed into one section in the classification (named medulloblastoma, histologically defined). Of note, associations exist between molecular signatures and morphological patterns, for example, all true desmoplastic/nodular MBs align with the SHH group [163].

Further to the above, new subgroups have emerged within the four main molecular groups. Four subgroups of SHH-MB and eight subgroups of non-WNT/non-SHH MB (groups 3 and 4) are now recognised. *Hill et al.* showed that MB groups and subgroups can affect the timing and pattern of disease relapse. In their study, patients with group 3 MB had significantly reduced times to relapse

while those with group 4 MB had a prolonged time to relapse suggesting the need for extended surveillance in the latter group [164]. Isolated local relapses were seen in SHH-MB tumours whereas groups 3 and 4 had distant relapses of disease. As is the case for the main molecular groups, the molecular subgroups can also support clinical prognostication and diagnosis [164]. Other studies have shown that patients with subgroup SHH-1 MB have poorer prognostic outcomes compared to those in subgroup SHH-2 MB, which can contribute to optimised treatment planning [165, 166].

In 2014, a location-based imaging approach to potentially distinguish molecular subgroups of medulloblastoma was described by Perreault *et al.* [167]. In their study, for example, group 3/4 tumours predominated within the midline 4th ventricle, WNT-MB tended to localise to the cerebellar peduncle/cerebellopontine angle and SHH-MB tumours were more commonly seen in the cerebellar hemispheres. Although helpful, this strategy is simplified and not definitive. Yeom *et al.* suggested ADC values and conventional MRI features might be combined to predict MB subgroups [168]. Given the molecular complexity, advanced imaging techniques using radiomics and deep-learning approaches could be future approaches to allow a more comprehensive radiological classification. *Perreault and Yeom* have since demonstrated a proof-of-concept application of radiomic profiling through a machine learning approach for predicting medulloblastoma subgroups, which describes radiomic features predicative of SHH and group 4 MBs [169].

WNT-MB make up 10% of all MBs and are frequently found in close association to the Foramen of Luschka, often forming broad contact with the brainstem [170]. Compared to other MBs there is increased porosity of the blood-brain barrier, and the tumours show avid enhancement [171]. The prognosis is excellent in children with this subtype with current combined surgical and adjuvant therapy achieving a survival rate of nearly 100% [172].

SHH-MB arise with a bimodal age distribution in infants and adults. SHH-MB are seen as solid, avidly enhancing masses with perilesional oedema reported as a helpful finding in one study [173]. MBs with extensive nodularity (which align with the SHH group) have demonstrated multiple small T2w cystic areas within the tumour in a ‘grape-like’ morphology on MRI [174]. Generally,

patient outcomes for SHH-MB are intermediate between WNT group and group 3 [1], however, prognostication within each subgroup is more complex and variable. Group 3 account for 25% of MBs, and group 4 are the largest molecular group making up 40% of all MBs [175]. Groups 3 and 4 are typically midline masses arising from the vermis. Group 3 tumours tend to be less well defined than group 4 and demonstrate more prominent enhancement [167].

A full review of the medulloblastoma subgroups is beyond the scope of this review. However, the role that neuroradiologists can play in assisting with the initial grouping and subgrouping over the coming years may become an area of rapid advancement. This is important given the drastically different prognostic and therapeutic implications depending on the tumour class involved. For example, WNT-MB show favourable outcomes with a 90% 5-year survival rate compared to group 3 tumours, for which survival is less than 50% [176].

Other CNS Embryonal Tumours

The previously defined tumour types in this family are *(1) Atypical teratoid/rhabdoid tumour (ATRT) and (2) Embryonal tumour with multi-layered rosettes (ETMR).* The new types which have now been *recognised in this family with molecular definitions are: (3) CNS neuroblastoma, FOXR2–activated, (4) CNS tumour with BCOR internal tandem duplication and the provisional type (5) Cribriform neuroepithelial tumour (CRINET) (introduced as a provisional type).*

In 2016, the WHO classification of embryonal tumours underwent substantial revision with the removal of the term primitive neuroectodermal tumour. Through molecular profiling Sturm *et al.* discovered four new CNS tumour types which have been previously described under the category of primary neuroectodermal tumours of the CNS [99]. CNS neuroblastoma, *FOXR2*–activated and CNS tumour with *BCOR* internal tandem duplication (CNS tumour *BCOR* ITD) are now included as distinct tumour types in the WHO 2021 classification and are described in more detail below.

1. CNS WHO5 now recognises three ATRT subtypes: ATRT-SHH, ATRT-TYR and ATRT-MYC [177].

   Imaging: Although much of the data is still preliminary, ATRT-SHH (Fig. 16) is believed to present throughout the brain (29% do not show enhancement), ATRT-TYR may show a

predilection for the cerebellum (with peripheral cysts in 94% of cases) and ATRT-MYC presents mostly supratentorial, but also in the spinal canal [178, 179]. Generally, the presence of restricted diffusion, peripheral cysts and haemorrhage may point to the ATRT (Fig. 16) although medulloblastoma is a differential. However, patient age remains most important to differentiate ATRT (most common embryonal tumour in children under 2 years) from medulloblastoma (much more common than ATRT in children above the age of 5 years).

2. ETMR was previously defined by alterations of the *C19MC* locus at 19q13.42 [180]. However, it has been recognised that they may instead harbour a *DICER1*–alteration which is almost always associated with DICER1 syndrome [181].
   Imaging: ETMRs show restricted diffusion, typical of embryonal tumours and sharp margins (Fig. 17); usually, haemorrhage is present but perifocal oedema absent [182]. Enhancement is variable and can be absent.

3. While a tumour called, CNS neuroblastoma was incorporated into the 2016 WHO classification based on histological features without molecular characterisation [183], the term has been repurposed as part of molecularly defined tumour type, *CNS neuroblastoma, FOXR2*–activated. The extent to which these differently defined but semantically related types overlap is unclear.
   Imaging: Holsten *et al.* showed in their case series that *FOXR2*–activated CNS neuroblastoma tends to present as a large supratentorial mass with mixed solid and cystic components and restricted diffusion (Fig. 18); enhancement is variable [184]. Tumours in this cohort showed relatively little mass effect despite their large size and had a sharply defined peripheral contour with central necrosis and a moderate amount of perilesional oedema.

4. *CNS tumour BCOR ITD* has been described as a tumour with a distinct methylation profile and characteristic internal tandem duplication in *BCOR*. From the limited literature it presents with a median age of diagnosis of 3.5 years with a balanced male: female ratio [185-187]. The cerebellar or cerebral hemisphere are the most frequently involved

locations with metastases generally absent at the time of diagnosis. At relapse however, leptomeningeal metastases and continuous spread along surgical tracts have been reported [188].

Imaging: On MRI, this tumour tends to appear as a solid, circumscribed mass in a superficial location with hyperintense signal on T2w (Fig. 19). The tumour does demonstrate restricted diffusion with variable and heterogenous contrast enhancement. Large internal cystic components, necrosis and intratumoral haemorrhage have been described [187]. MR spectroscopy has been reported in one patient so far (high choline peak, reduced NAA and a lipid/lactate doublet) [189].

5. *Cribriform neuroepithelial tumour (CRINET)* has been introduced as a provisional type in the WHO 2021 classification. CRINET represents a *SMARCB1*-deficient non-rhabdoid tumour with molecular similarities to the ATRT-TYR subgroup, but distinct histopathological features and a favourable long-term outcome compared to ATRT-TYR [190].

   Imaging: The limited literature on CRINET describes tumours in the paediatric population aged between 10-26 months with a male predilection [191]. Imaging has been reported as a large intraventricular mass with both solid and cystic components demonstrating heterogenous enhancement and hydrocephalus as a presenting feature [191, 192].

Pineal Tumours

Pineal gland tumours include *Pineocytoma* (CNS WHO grade 1), *Pineal parenchymal tumour of intermediate differentiation* (CNS WHO grade 2–3), *Pineoblastoma* (CNS WHO grade 4) and. *Papillary tumour of the pineal region* (CNS WHO grade 2–3). A new addition under this classification is the *Desmoplastic myxoid tumour of the pineal region, SMARCB1-mutant (no grade assigned yet)*. It shows epigenetic similarities with ATRT-MYC, presents in adolescents and adults and has an intermediate prognosis [194].

In WHO CNS5, pineoblastomas are subdivided into 4 molecular subtypes which are beyond the scope of this review article [193]. Suffice to say, no imaging associations have been made yet with any specific molecular subtypes.

Imaging: Pineoblastomas are typically large tumours causing hydrocephalus in most cases. Due to their hypercellular nature, they often show diffusion restriction. Enhancement is usually present in solid tumour components but may be absent [xx]. ETMR presenting in this region are a differential diagnosis in very young children.

Meningiomas

Meningioma is now considered a single type with 15 subtypes to reflect the wide morphological spectrum. Several molecular markers assist with the classification and grading of meningiomas e.g., *SMARCE1* and clear cell subtype or *BAP1* relating to rhabdoid and papillary subtypes. It is now emphasised that the criteria defining atypical or anaplastic (i.e., grade 2 or 3) should be applied regardless of the underlying subtype [3]. Molecular features can also be used for prognostication in meningioma. Meningiomas with *TERT* promoter mutations for example, show elevated rates of malignant transformation, decreased time to disease relapse and shorter overall survival times compared to those tumours without such mutations [195-197]. Changes in cell cycle regulating genes *CDKN2A* and *CDKN2B* have also been shown to commonly occur in recurrent meningiomas and are associated with generally poorer outcomes [198, 199].

Mesenchymal / Non-Meningothelial Tumours

The current classification has attempted to align the terminology of mesenchymal, non-meningothelial tumours with their counterparts in the 'WHO Blue Book on Bone and Soft Tissue Tumours'. New types of tumours included in this version include i*ntracranial mesenchymal tumour, FET-CREB fusion-positive* (provisional); *CIC-rearranged sarcoma*; and *primary intracranial sarcoma, DICER1-mutant.* Haemangiopericytoma has not been included and is now referred to as only solitary fibrous tumour.

Cranial and peripheral nerve tumours

Paragangliomas are now included under nerve tumours given they derive from neuroendocrine cells of the autonomic nervous system. Paraganglioma of the cauda equina has become a distinct tumour type given DNA methylation differences. Melanotic schwannoma has been renamed *malignant melanotic nerve sheath tumour* in accordance with the soft tissue classification. A new subtype of neurofibroma is included termed *atypical neurofibromatous neoplasm of unknown*

biological potential (ANNUBP). This lesion is an NF1-associated tumour with features of malignant transformation that are quantitatively insufficient for a definitive diagnosis of *Malignant peripheral nerve sheath tumour (MPNST).*

Haematolymphoid tumours

WHO CNS5 only includes those lymphoid and histiocytic tumour types that occur relatively frequently within the central nervous system or have specific molecular features when occurring within the CNS.

Germ cell tumours

No significant changes were proposed in this tumour category.

Tumours of the Sellar Region

Adamantinomatous craniopharyngioma and *Papillary craniopharyngioma* are now considered distinct tumour types, given multiple differences in demographics, radiologic features and molecular profiles [200, 201]. Pituicytoma, granular cell tumour and spindle cell oncocytoma are grouped as related tumour types [202].

WHO CNS5 divides pituitary adenomas by adenohypophyseal cell-lineage, following, the endocrine WHO classification. WHO CNS5 includes the term *Pituitary neuroendocrine tumour* (PitNET) [203]. Finally, *Pituitary blastoma*, an embryonal neoplasm of infancy, has been newly added. The tumour may extend into the suprasellar region and cavernous sinus [WHO CNS5 online].

Implications for neuroradiological practice

Given the growing focus on brain tumour molecular details, the diagnostic strategy is becoming increasingly complex, and the remit of the neuroradiologist appears less clear. Imaging approaches and reporting standards continue to evolve in support of an integral brain tumour diagnosis. In future, this would ideally include detailed radiomic correlations in parallel with the latest WHO

definitions. This clinical need, however, diverges from the published imaging literature, which is predominantly based on older grouping and nomenclature.

It is clear that the imaging features of many newly defined molecular tumour types are partially recognised, non-specific or yet unknown.

Whilst the fundamental purposes of imaging in the initial diagnosis such as lesion localisation, estimating disease extent and to aid surgical planning remain unchanged, there is now a requirement to develop imaging biomarkers for the revised and new tumour groups. Particularly for the rarer neoplasms, research across institutions with pooling of data may create opportunities for identifying and validating typical features.

Conclusion

The updated WHO CNS5 classification includes new and revised tumour categories, families, types and subtypes that impact the radiological strategy. As such, the common practice of an image-based estimation of ‘grade’ can be fraught with errors, and in some circumstances becomes irrelevant. It is essential for neuroradiologists to become familiar with the new classification system and, where possible, support its application through further research into meaningful radiomic correlations.

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Figures

Fig. 1. Overview of the WHO Classification of CNS Tumours 2021. Note, new tumour types are in grey cells.

Fig. 2. Flow chart depicting changes to adult gliomas between 2016 and 2021.

Fig. 3. Adult-type gliomas: **Astrocytoma, IDH-mutant.** MRI of three different patients with CNS WHO grade 2, 3 and 4 tumours. This figure illustrates changes in nomenclature between the 2016 and 2021 classifications.
(A-C) A 60-year-old man previously diagnosed with Grade II diffuse astrocytoma, IDHmut. WHO 2021 Integrated diagnosis (Molecular: IDHmut, 1p/19q retained, no CDKN2A deletion): **Astrocytoma, IDH-mutant, CNS WHO grade 2**.
MRI shows moderately homogenous high T2w signal (A) which suppresses on FLAIR (B) with faint intrinsic enhancement on T1w-CE (C).
(D-F) A 54-year-old man previously diagnosed with Grade III anaplastic astrocytoma, IDHmut. WHO 2021 integrated diagnosis (Molecular: IDHmut, 1p/19q retained, no CDKN2A deletion): **Astrocytoma, IDH-mutant, CNS WHO grade 3**.
The left insular and temporal lobe tumour demonstrates homogenous high signal on T2w (D) and partial suppression on FLAIR (E) with faint enhancement on T1w-CE (F).
(G-I) A 32-year-old woman previously diagnosed with Grade IV Glioblastoma, IDHmut. WHO 2021 Integrated diagnosis (Molecular: IDHmut, 1p/19q retained, CKN2A status unknown): **Astrocytoma, IDH-mutant, CNS WHO grade 4**.
The left frontal, well-marginated lesion exhibits heterogenous high T2w signal (G) with partial suppression on FLAIR (H). Demonstrates a region of irregular peripheral enhancement with central necrosis on T1w-CE (I).

Fig. 5. Adult-type gliomas: **Oligodendroglioma, IDH-mutant and 1p/19q-codeleted**. MRI of two patients with WHO CNS grade 2 and 3 tumours.
(A-C) A 48-year-old woman previously diagnosed with Grade II oligodendroglioma, IDHmut. WHO 2021 Integrated diagnosis: **Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2**.
The left frontal lobe, incompletely marginated lesion demonstrates mildly heterogenous high T2w signal (A) without FLAIR suppression (B) and with subtle intrinsic T1-shortening, but without contrast enhancement) (C).
(D-F) A 29-year-old man previously diagnosed with Grade III anaplastic oligodendroglioma, IDHmut. WHO 2021 Integrated diagnosis: **Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 3**.
The right frontoinsular tumour demonstrates mildly heterogenous high T2w signal (D) without suppression on FLAIR (E), partial enhancement and a small focus of necrosis on post contrast T1w (F).

Fig. 5. Adult-type gliomas: **Glioblastoma, IDH-wildtype**. MRI of three different patients with CNS WHO grade 4 tumours, previously classified as grade II, III and IV according to WHO 2016.

(A-C) A 66-year-old male previously diagnosed with Grade II diffuse astrocytoma. WHO 2021 Integrated diagnosis (Molecular: IDHwt, TERTmut, EGFRwt CDKN2A/B no loss): **Diffuse glioma, IDH-wildtype with molecular profile favouring Glioblastoma.***
The left temporal, moderately well marginated, homogenous high T2w signal lesion (A) demonstrates partial suppression on FLAIR (B), increased intra-sulcal vascular enhancement, but no pathological parenchymal enhancement or necrosis (C).
(D-F) A 70-year-old man previously diagnosed with Grade III anaplastic astrocytoma. WHO 2021 Integrated diagnosis (Molecular: IDHwt, TERTwt, EGFR amplification, PTENmut): **Glioblastoma, IDH-wildtype (CNS WHO grade 4)**.
The moderately heterogenous right temporal and occipital tumour exhibits high signal on T2w and FLAIR (D,E) and demonstrates ill-defined, multifocal enhancement without radiological evidence of necrosis (F).
(G-I) A 35-year-old man previously diagnosed with Grade IV glioblastoma. WHO 2021 Integrated diagnosis (IDHwt, TERTmut, EGFR amplification, PTENmut, CDKN2A/B loss): **Glioblastoma, IDH-wildtype (CNS WHO grade 4)**.
The left temporal, heterogenous mixed T2w signal mass (G,H) demonstrates peripheral irregular enhancement with central necrosis (I).
*Note: *Whilst in WHO CNS5 the presence of a TERT promoter mutation in an IDH wild type glioma allows for the diagnosis of glioblastoma, it is important to be aware that grade II IDH wild type gliomas with isolated TERT promoter mutations behave less aggressively than other molecular glioblastomas with a median overall survival of 88 months (see "adult-type diffuse gliomas" [204].*

Fig. 6. Paediatric-type diffuse high-grade gliomas: **Diffuse midline glioma, H3 K27–altered** (CNS WHO grade 4).
A 6-year-old boy referred by ophthalmology with visual disturbance, weight gain and headaches. Molecular testing: H3 K27me3 retained staining in some cells, homozygous loss of CDKN2A/B with EGFR mutation.
T2w (A, B), DWI (C) and T1w-CE (D) show an expansile, mildly T2w hyperintense, bithalamic tumour extending into the brainstem. There is associated hydrocephalus. The mass only showed small foci of faint enhancement (arrow).

Fig. 7. Paediatric-type diffuse high-grade gliomas: **Diffuse hemispheric glioma, H3 G34–mutant** (CNS WHO grade 4).
A 14-year-old boy with a 4-week history of left-sided weakness, slurred speech and loss of balance. Immunohistochemistry: H3.3 G34R nuclear staining. Molecular: IDH-wildtype.
FLAIR (A-C), DWI (D) and T1w-CE (E, F) show multifocal areas of cortical and subcortical FLAIR signal abnormality involving the left peri-rolandic and temporal regions as well as the right cingulate, cuneus and insular regions (arrows). Several of these areas show patchy enhancement and mild restricted diffusion.

Fig. 8. Paediatric-type diffuse high-grade gliomas: **Infant-type hemispheric glioma**.
A 14-week-old boy presented with symptoms of sepsis, seizures, poor feeding and vomiting. Fusion panel sequencing: TRIM24-MET fusion.
T2w (A), T1w-CE (B-C) and ADC (D) show a large right-sided MCA and ACA territory infarct. The right frontal lobe solid and cystic tumour is hyperintense on T2w. Assessment of diffusion

characteristics on ADC (D) are hampered by presence of haemorrhage SWI (E) in the tumour and ventricular system, but diffusion of solid tumour components is facilitated. The tumour infiltrates the adjacent frontal horn. There is intraspinal leptomeningeal disease (arrows in C).

Fig. 9. Paediatric-type diffuse low-grade gliomas: **Diffuse astrocytoma, *MYB*- *or MYBL1*-altered** (CNS WHO grade 1).
An 18-month-old girl presents with a 4-day history of episodes of facial distortion and drooling, seizures. Methylation profiling: low grade glioma, *MYB/MYBL1*.
T2w (A) shows a diffusely infiltrating tumour of the left parietal and temporal white matter. There is mass effect on basal ganglia, thalamus and corpus callosum with midline shift. There is peripheral high FLAIR signal (B) without enhancement on T1w-CE (C) or restricted diffusion on ADC (D).

Fig. 10. Paediatric-type diffuse low-grade gliomas: **Angiocentric glioma** (CNS WHO grade 1).
An 8-year-old boy presenting with recurrent seizures with a focal semiology and behavioural changes. Methylation class low grade glioma *MYB/MYBL1*. *QKI-MYB* fusion was detected using the RNA fusion panel.
T2w (A, B) show a cortical/subcortical lesion in the left middle frontal gyrus without restricted diffusion (C) or enhancement on T1w-CE (D). No blood product present (SWI not shown).

Fig. 11. Glioneuronal tumours: **Multinodular and vacuolating neuronal tumour** (CNS WHO grade 1, presumptive diagnosis).
A 39-year-old woman with a 26-year history of occasional seizures.
T2w (A, B) demonstrate a left para-midline, multi-cystic lesion centred on the subcortical white matter of the left cingulate gyrus. The lesion demonstrates no enhancement on T1w-CE (C) and the cystic regions suppress on FLAIR (D).

Fig. 12. Glioneuronal tumours: **Diffuse glioneuronal tumour with oligodendroglioma-like features and nuclear clusters** (provisional entity).
An 11-year-old boy presented with seizure.
A mass in the right medial frontal lobe shows heterogeneous hyperintensity on T2w- (A) and FLAIR (B). Small cysts are noted. Diffusion shows heterogenous signal but a small focus of low ADC (C). The tumour shows small foci of enhancement on T1w-CE (D).

Fig. 13. Glioneuronal tumours: **Diffuse leptomeningeal glioneuronal tumour**.
A 15-year-old girl presented with a 3-month history of back pain radiating to both legs.
T2w (A) shows a multi-septated cystic lesion expanding the lower thoracic cord and conus medullaris. Small ovoid focus of less hyperintense T2w signal abnormality within the anteroinferior aspect of the lesion shows pathological enhancement on T1w-CE (B). Intrinsic cord signal abnormality is seen extending above the level of the cystic lesion into the midthoracic cord.

Fig. 14. Ependymal tumours: **Supratentorial ependymoma, *ZFTA* fusion-positive**.
A 6.5-year-old girl presented with a 6-week history of headache and weight loss, squint of the left eye, abdominal pain and vomiting. Clinically she showed right 6^{th} nerve palsy.

T2w (A), coronal FLAIR (B), sagittal T1w-CE (C) and ADC (D) show a left parietal mass causing significant midline shift and mass effect on the corpus callosum. Restricted diffusion is present. The mass also shows avid, heterogenous enhancement of the periphery and solid tumour components.

Fig. 15. Ependymal tumours: **Posterior fossa group A (PFA) ependymoma**.
A 14-month-old girl presented with 1 month history of progressive weakness and frequent falls, has been unwell, lethargic and vomiting for 11 days, choking on food and right-sided torticollis, she was finally unable to sit or walk. Clinically, she showed quadriparesis and nystagmus.
Coronal T2w (A), FLAIR (B), DWI (C) and T1w-CE (D) show a large tumour centred on the inferior aspect of the posterior fossa causing obstructive hydrocephalus. T2 signal intensity and enhancement are inhomogeneous. Prominent vessels are noted. DWI shows neither diffusion restriction or increased diffusivity.

Fig. 16. Embryonal tumours: **Atypical teratoid/rhabdoid tumour, subtype AT/RT-SHH** (CNS WHO grade 4).
(A-D) An 11-month-old boy with hydrocephalus. *SMARCB1* mutation. Methylation profiling showed AT/RT, subclass SHH.
T2w (A), DWI (B) and T1w-CE (C-D) show a large, lobulated intraventricular lesion expanding the 3rd ventricle with extension into the right lateral ventricle and associated hydrocephalus. The lesion demonstrates restricted diffusion, but only minimal enhancement. Intraspinal metastases are present.
(E-H) A 16-month-old boy presented with difficulty walking and vomiting. Molecular: *SMARCB1* mutation, methylation subclass SHH.
T2w (A), T1w-CE (B), ADC (C) and SWI (D) show a heterogenous lesion expanding the 4th ventricle which contains multiple cysts. The lesion is characterised by minimal focal enhancement, restricted diffusion, and microhaemorrhages.

Fig. 17. Embryonal tumours: **Embryonal tumour with multi-layered rosettes**.
2-year-old girl presented with left-sided weakness. Methylation class of an embryonal tumour with multi-layered rosettes, C19MC-altered
T2w (A), FLAIR (B), DWI (C) and T1w-CE (D) show a circumscribed mass in the pons that is hyperintense on FLAIR and T2w sequences. The lesions demonstrate marked restricted diffusion without enhancement.

Fig. 18. Embryonal tumours: **CNS neuroblastoma, *FOXR2*–activated**.
A 5-year-old girl. Methylation class, CNS neuroblastoma with *FOXR2* activation
T2w (A) and FLAIR (B) show a large, circumscribed mass centred on the left striatocapsular region with inferior extension into the suprasellar cistern. The tumour is effacing the third ventricle and the lateral ventricles are dilated. There is marked restricted diffusion (C) and heterogeneous enhancement on T1-CE (D).

Fig.19. Embryonal tumours: **CNS tumour with *BCOR* internal tandem duplication**.
A 5-year-old boy presented with vomiting and headaches. Methylation class of CNS high-grade neuroepithelial tumour with *BCOR* alteration.

T2w (A), FLAIR (B, D) show a hyperintense mass located within the peripheral aspect of the right cerebellar hemisphere. Linear areas of contrast enhancement on T1w-CE (C) are present. There is partial effacement of the 4^{th} ventricle and associated hydrocephalus.

Tables

Table 1. Key mutations and imaging features in adult gliomas.

Tumour Type	**Genetic marker**	**Description**	**Known imaging features**
Astrocytoma, IDH mutant	*IDH1, IDH2* (isocitrate dehydrogenase 1 and 2)	Enzymes in Krebs cycle, involved in isocitrate to alphaketoglutarate and NADPH production	Relatively circumscribed homogenous high T2w signal supratentorial lesions most commonly seen in the frontal or temporal lobes. T2-FLAIR mismatch with FLAIR hyperintense rim. Grade 2 typically non-enhancing however higher lesions can show enhancement and appear more heterogeneous.
	ATRX (Alpha thalassemia retardation syndrome X-linked)	Regulates cell cycle and telomere length. Modulates p53 in cancer.	
	TP53 (Tumour protein p53)	Tumour suppression gene that regulates cell cycle	
	CDKN2A/B (Cyclin-dependent kinase inhibitors)	Genes located on chromosome 9 which code for tumour suppressor genes p14, p15 and p16. Their presence makes even histologically low-grade tumours WHO grade 4.	
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	*IDH1, IDH2*	Enzymes in Krebs cycle, involved in isocitrate to alphaketoglutarate and NADPH production	Supratentorial lesions with a frontal lobe predilection and infiltrative margins.
	1p/19q	Occur as combined deletion of entire	

		chromosome arms 1p/19q after unbalanced translocation between chromosomes between chromosomes 1 and 19 [t(1:19)(q10;p10)] [205]	Heterogenous with calcification typically present. T2/FLAIR mismatch sign not a feature. Varying degrees of enhancement which does not correlate well with tumour grade.
	TERT promoter	Gene located on chromosome 5p15.33, and encodes for the catalytic subunit of telomerase [206]	
	NOTCH1	Encodes a transmembrane protein that functions in multiple developmental processes and the interactions between adjacent cells.	
Glioblastoma, IDH-wildtype	IDH-wildtype (isocitrate dehydrogenase 1 and 2)	Enzyme in Krebs cycle, involved in isocitrate to alphaketoglutarate and NADPH production	Heterogenous T2w hyperintense mass with enhancement and restricted diffusion within the solid components with extensive perilesional signal abnormality. Multiple areas of susceptibility artefact in keeping with intralesional haemorrhage.
	TERT promoter	Gene located on chromosome 5p15.33, and encodes for the catalytic subunit of telomerase	
	Chromosomes 7/10		
	EGFR (epidermal	Oncogene encoding a tyrosine kinase resulting	

	growth factor receptor)	in increased DNA synthesis	*Note, molecularly-defined glioblastomas may lack necrosis or parenchymal enhancement on magnetic resonance imaging (MRI).*

Table 2. Key mutations and imaging features in paediatric gliomas.

Tumour Type	**Genetic marker**	**Description**	**Known imaging features**
Diffuse astrocytoma, *MYB/MYBL1*-altered	*IDH1*, *IDH2*	Enzymes in Krebs cycle, involved in isocitrate to alphaketoglutarate and NADPH production	Supratentorial with subcortical involvement, temporal lobe predilection followed by frontal and occipital locations. Heterogenous hyperintense or mixed signal intensity on FLAIR without enhancement or diffusion restriction. *Note, imaging descriptors are based on small number of studied cases to date.*
	ATRX		
	TP53	Tumour suppression gene that regulates cell cycle	
	CDKN2A/B		
Diffuse low-grade glioma, MAPK pathway-altered MAPK (mitogen-activated protein kinase) *(encompasses tumours of an astrocytic or*		MAP kinase pathway is critical to normal development and deregulated in a multitude of cancers and is situated downstream of tyrosine kinase receptors	Specific imaging features not well defined at present.
	FGFR1 (fibroblast growth factor 1)	Group of membrane receptors involved in many cellular processes including proliferation and migration	

oligodendroglial morphology)	*BRAF*	One of three RAF kinases which acts as downstream effector in MAPK pathway of growth factor signalling leading to cell cycle progression	
Diffuse midline glioma, H3 K27-altered	H3 K27	Refers to mutations at codon 27 (lysine to methionine, K27M) of the *H3F3A* or *HIST1H3B/C* genes encoding the histone variants, H3.3 or H3.1	Brainstem, thalamic (can be bithalamic), cerebral midline or spinal cord locations. More rarely seen in the hypothalamus, pineal region or cerebellum. T2w hyperintense with variable enhancement. Minimal ADC and peri-tumoural ADC values may be lower in H3 K27M-mutant gliomas compared with H3 K27M-wildtype gliomas.
	ACVR1	Gene that encodes for the *ALK2*, a receptor in the bone morphogenetic protein (BMP) signalling pathway	
	PDGFRA (platelet derived growth factor receptor alpha)	Encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin.	
	EZHIP (EZH inhibitory protein)	Protein encoding gene which regulates activity of histones and mediates global *H3K27me3* reduction [207]	

Diffuse hemispheric glioma, H3 G34-mutant	H3 G34	Defined by a recurrent glycine to arginine or valine substitution at codon 35 of the histone H3.3 gene *H3F3A*, corresponding to amino acid 34 of the mature H3.3 protein	Hemispheric location (typically frontoparietal in a cortical or subcortical location) with occasional extension to midline structures typically hyperintense on T2w/FLAIR. Variable enhancement with mass effect. Typically shows restricted diffusion. Intralesional haemorrhage and calcification can be present on SWI sequence.
	TP53	Tumour suppression gene that regulates cell cycle	
	ATRX (Alpha thalassemia retardation syndrome X-linked)	Regulates cell cycle and telomere length. Modulates p53 in cancer	
Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype	H3-wildtype	Lacks the histone substitution detailed above	Supratentorial, brainstem and cerebellar locations (most commonly in the cerebral hemisphere). Can be poorly marginated heterogenous lesion that is hyperintense on FLAIR with irregular enhancement and restricted diffusion in the
	PDGFRA	Encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin	
	MYCN		

	EGFR (epidermal growth factor receptor)	Oncogene encoding a tyrosine kinase resulting in increased DNA synthesis	solid components or relatively well demarcated. Variable perilesional signal abnormality.