The WHO 2016 Classification of Tumours of the CNS: What the Paediatric Neuroradiologist Needs to Know

Poster No.: C-2795
Congress: ECR 2018
Type: Educational Exhibit
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Keywords: Molecular, genomics and proteomics, Cancer, Staging, MR, Pediatric, CNS
DOI: 10.1594/ecr2018/C-2795

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Learning objectives

1. Understand the reasons behind the reorganisation of the WHO 2016 Classification of Tumours of the Central Nervous System.
2. Learn some of the common genetic mutations that underpin these changes.
3. Use selected radiological features to suggest genetic classification underlying common paediatric tumours.
Background

The characterisation of tumours of the central nervous system has, in the past, predominantly been based on histological features including light microscopy of haematoxylin and eosin-stained sections and immunohistochemical detection of proteins. However, genetic analysis is of growing importance. This is reflected in the WHO 2016 Classification of Tumours of the Central Nervous System which presents restructuring on a molecular basis [1]. A review of selected cancer imaging acquired at Great Ormond Street Hospital with known histological and molecular characterisation is presented to illustrate the new classification.
Findings and procedure details

**Nomenclature**

CNS tumours should be named with the histopathological name followed in certain cases by one or more genetic features, for example: Medulloblastoma, SHH-activated, TP53-mutant. For certain tumours, the term "wildtype" can be used in certain instances where a specific genetic mutation has been confirmed not to be present, for example Glioblastoma, IDH-wildtype. When a subtype cannot be confirmed, for example when the material is insufficient or the technique is not locally available, the designation Not Otherwise Specified (NOS) is given.

**Diffuse Gliomas**

An entity of particular relevance in children is the diffuse midline glioma, H3 K27M-mutant, which represents the majority of diffuse intrinsic pontine gliomas (Figures 1-2). H3 K27M-mutant type includes most tumours previously referred to in the clinical literature as diffuse intrinsic pontine glioma (DIPG). This entity, typically of the thalamus, pons or spinal cord, is characterised by K27M mutations in one of the histone H3 genes (typically H3F3A, HIST1H3B, HIST1H3C gene), a diffuse growth pattern, and a midline location [2]. It carries a very poor prognosis. Of note, there is increasing data that this tumour has been under recognised in adults.

The terms protoplasmic astrocytoma and fibrillary astrocytoma have been removed. Gliomatosis cerebri is no longer considered a distinct entity but is regarded as a growth pattern of other glial tumours.

**Glioblastoma**

Glioblastoma is the most aggressive malignant primary brain tumour. It remains almost universally incurable in both children and adults. Glioblastomas are classified based on IDH mutations into glioblastoma-IDH-wild-type, glioblastoma-IDH-mutant and glioblastoma-NOS. IDH-mutant status confers a better prognosis, less necrosis, and tends to occur in a younger age group (Figure 3).

A new entity with a predilection for children and young adults is the WHO IV epithelioid glioblastoma. These tumours typically present as diencephalic or superficial cerebral masses [3]. They appear similar to glioblastoma on imaging. The main differential diagnosis is atypical teratoid / rhabdoid tumour (AT/RT), distinguished by universal lack
of INI1 expression. In addition BRAF-V600E mutations are commonly found in epithelioid glioblastoma (unlike other types of glioblastoma) [4]. The prognosis is worse even than glioblastoma, and systemic metastases are sometimes seen.

**Oligodendrogliomas and oligoastrocytomas**

The WHO 2016 classification requires demonstration of IDH gene family mutation and whole-arm losses of 1p and 19q (1p/19q codeletion) for a diagnosis of oligodendroglioma and anaplastic oligodendroglioma. It is notable, however, that paediatric tumours that histologically resemble oligodendroglioma often lack these features. These should currently labelled oligodendroglioma until further research has been conducted to understand this phenomenon.

The new classification suggests that the diagnosis of oligoastrocytoma should be made less commonly, as most tumours with histological features of astrocytic and oligodendroglial components can be classified as either astrocytoma or oligodendroglioma using genetic testing. WHO grade II oligoastrocytoma and WHO grade III anaplastic oligoastrocytoma therefore are designated NOS.

**Embryonal Tumours**

**Medulloblastoma**

The histological classification is already well defined and includes: classic, anaplastic/large cell, desmoplastic/nodular and extensive nodular variants. In the WHO 2016 classification, medulloblastomas are classified in to (1) WNT-activated (MBWNT); (2) SHH activated (MBSHH), TP53 wildtype; (3) SHH - activated (MBSHH), TP53 mutant; (4) Non -WNT/Non -SHH medulloblastoma [5]. The latter type can be subdivided into "group 3" and "group 4" with the aid of DNA methylation or mRNA expression profiling [6].

Tumor location and enhancement pattern has been shown to be somewhat predictive of molecular subgroups of paediatric medulloblastoma, with two-thirds of tumours being correctly categorised in one study [7]. The most common type is Group 4 [8] [6] (Figure 4). They have a predilection for males, with a 2:1 male to female ratio. Most commonly they have classic histology. They also have typical radiological features: they are midline masses arising from the vermis and well-defined with limited contrast enhancement. Group 3 are slightly less common than Group 4 and carry similar radiological and prognostic features to Group 4, appearing as midline masses arising from the vermis. They are slightly less well defined radiologically with more prominent enhancement. The SHH subtype occur with approximately the same incidence as Group 3 (Figure 5).
They occur most commonly in adults and infants and less frequently in children. They more commonly arise peripherally in the cerebellar hemisphere, and often have multiple enhancing nodules and cystic components. The WNT subtype is the least common and has the best prognosis (Figure 6). They often arise from the middle cerebellar peduncle. They commonly extend to the cerebellopontine angle cistern and through the foramen of Luschka.

An entity of particular note is the medulloblastoma, SHH-activated and TP53 mutant [8]. The clinical outcomes for this subtype of medulloblastoma are very poor. These patients carry a significant risk of having a germline TP53 mutation and should be offered genetic counselling.

The medulloblastoma, large cell/anaplastic subtype is aggressive and recognized readily by its histological and cytological features in H&E-stained sections. It is associated with a high relapse risk and poor outcome. Radiologically it is often associated with higher ADC, less cysts, and, and ring enhancement [7] (Figure 7).

Other embryonal tumours

This group has undergone substantial changes. The term primitive neuroectodermal tumour or PNET has been removed. A new category, CNS embryonal tumour, NOS, includes tumours previously designated as CNS PNET (amongst others). It is expected that new molecular markers will in the future make this group redundant.

The term embryonal tumour with multilayered rosettes (ETMR) incorporates the now defunct entities of embryonal tumour with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, some medulloepitheliomas, and some CNS Primitive neuroectodermal tumour (PNET). The reclassification was driven by the recognition that these tumour types commonly exhibit amplification of the C19MC region on chromosome 19 (19q13.42). ETMRs are LIN28A positive, but some ATRTs and other tumours may (rarely) also be LIN28A positive so it is necessary to confirm C19MC amplification for full integrated WHO diagnosis "ETMR, C19MC altered" (eg. by FISH). C19MC-amplified tumours include the lesions previously known as ETANTR (embryonal tumours with abundant neuropil and true rosettes, but also referred to as embryonal tumours with multilayered rosettes), ependymoblastoma, and, in some cases, medulloepithelioma. In the absence of C19MC amplification, a tumour with histological features conforming to ETANTR/ETMR should be diagnosed as an embryonal tumour with multilayered rosettes, NOS, and a tumour with histological features of medulloepithelioma should be diagnosed as medulloepithelioma. ETMR most commonly occurs in children under 4 years and is more common in girls (unlike other CNS embryonal tumours in which gender distribution is equal) [9]. They are most common supratentorially and appear as a large demarcated
solid mass with patchy or no contrast enhancement. There is often significant mass effect (Figures 8, 9).

The atypical teratoid/rhabdoid tumour (AT/RT) is now defined by alterations in SMARCB1 (INI1) or rarely SMARCA4 (BRG1). ATRT occurs most commonly in children under 3 and has aggressive radiological features [10] (Figure 10). It may be supra- or infratentorial. It often has cysts and haemorrhage and commonly presents with dissemination. 'CNS embryonal tumour with rhabdoid features' is now the term used for tumours that have histological features of AT/RT without the specific genetic alterations and also when INI1 / SMARCA4 status cannot be tested.

**Ependymal Tumours**

It is recognised that the grading of ependymomas using existing WHO criteria is difficult and of questionable prognostic and therapeutic utility. It is expected that continuing studies of the molecular characteristics (particularly DNA methylation profiling) of ependymomas will provide more precise and objective means of classification. The RELA-fusion positive ependymoma is a new subtype. Unlike RELA-fusion negative ependymomas, which are predominantly infratentorial, these tumours occur most commonly supratentorially (Figure 12). These carry a poor prognosis. The term cellular ependymoma has been deleted in the 2016 classification. The anaplastic clear cell ependymoma is an existing subtype with a have high proliferative rate and a greater tendency to infiltrate surrounding brain or disseminate into cerebrospinal fluid causing drop metastases (Figure 13). Myxopapillary ependymoma is a fairly rare glioma that develops from the spinal part of the filum terminale (Figure 14). It is rare in childhood.

**Neuronal and mixed neuronal-glial tumours**

The diffuse leptomeningeal glioneuronal tumour is a rare tumour most commonly seen in children and adolescents. It presents with thick nodular leptomeningeal enhancement [11] (Figure 15). Hydrocephalus is common due to subarachnoid tumour accumulation. Subpial cysts may be seen over the basal surfaces of the cerebral hemispheres. BRAF fusions and deletions of chromosome arm 1p, sometimes in addition to 19q. IDH mutations are absent.

The multinodular and vacuolated tumour (MNVT) is an increasingly recognised cytoarchitectural pattern that appears as small 'bubbly' appearing indolent subcortical tumours [12] (Figure 16). They may present with seizures, although many are asymptomatic. Further research needs to be conducted to understand these entities.
Fig. 1: Diffuse midline glioma H3K27M-mutant in the pons and right cerebellar hemisphere in a 2-year-old. MRI: T2WI sagittal, T2WI axial.

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**Fig. 2:** Diffuse midline glioma H3K27M-mutant in a 7-year-old. MRI: T2WI coronal, T2WI axial, FLAIR axial. The tumour is centred on the pons with extension to the right cerebellar hemisphere and right midbrain. As is in this case, it is typically non-enhancing. Associated obstructive hydrocephalus is present.

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![MRI images](image1)

**Fig. 3:** Right temporal glioblastoma, IDH-wild type in a 6-year-old. (a) MRI: T2WI axial, DWI, T1WI coronal with gadolinium. (b) Stained light micrograph of tumour tissue. Histologically the appearances were of a high grade tumour with neuronal and glial differentiation.

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Fig. 4: Medulloblastoma Group 4 (non WNT/non SHH). (a) MRI: Sagittal T1WI + Gadolinium, Axial DWI, Coronal FLAIR. (b) Stained light micrograph of tumour tissue.
Description: There is a large predominantly solid mass with cystic spaces located in the fourth ventricle with extension via the left foramen of Luschka and foramen of Magendie. The mass has diffusion restriction, high perfusion and heterogeneous enhancement. There is marked localised mass effect on the brainstem, effacement of the pre pontine/premedullary cisterns and resultant acute obstructive hydrocephalus. Group 4 is the most common medulloblastoma subtype and typically arise, as in this case, in the vermis. They are common in children, occur not infrequently in adults, but are rare in infants. They tend to enhance to a limited extent (this example is uncommon in this regard). They have a poor prognosis (better than group 3, but worse than WNT and SHH types), and CNS metastases is common.

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**Fig. 5:** Medulloblastoma, SHH-activated TP53-wild type in a 3-year-old. (a) MRI: Sagittal/Axial/Coronal T1WI with gadolinium contrast enhanced. (b) Stained light micrograph of tumour tissue. SHH ("Sonic Hedgehog") is the second most common tumour type after "group 3" and are found most commonly in adults and infants but not in children. They are located most often in the cerebellar hemispheres and less commonly in the vermis. They have intermediate prognosis in comparison to other medulloblastomas (better than group 3 tumours, worse than WNT subtypes). The best outcomes are seen in infants, with decreasing survival correlating with age.

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Fig. 6: Medulloblastoma, WNT-activated. (a) MRI: T2WI axial, ADC, and T1WI with gadolinium contrast. (b) Stained light micrograph of tumour tissue showing classic histology.

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Fig. 7: Anaplastic medulloblastoma, SHH-activated, TP53 mutant in a 9-year-old. (a) MRI: T2WI axial, T1WI Sagittal with gadolinium. (b) Stained light micrograph of tumour tissue.

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Fig. 8: Infratentorial embryonal tumour with multilayered rosettes C19MC-altered in a 2-year-old. (a) MRI: Axial T2WI, DWI, Sagittal T1WI with gadolinium. (b) Stained light micrograph of tumour tissue. The tumour appears as a large, demarcated, solid mass featuring patchy or no contrast enhancement, with surrounding edema, often with significant mass effect. A minority of the reported cases have shown cystic components and microcalcifications. There is usually patchy or no contrast enhancement. The prognosis is very poor.

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**Fig. 9:** Pontine embryonal tumour with multilayered rosettes C19MC-altered in a 3-year-old. MRI: T1WI axial with gadolinium contrast, T2WI axial.

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Fig. 10: Atypical Teratoid / Rhabdoid Tumour in a 7-year-old. (a) MRI: T2WI axial, DWI. (b) Stained light micrograph of tumour tissue. The MRI shows a solid and partly cystic enhancing right frontal lobe tumour with an exophytic solid component. The solid component has restricted diffusion. There is a little peritumoral oedema. Two medial cystic components encroach on the right lateral ventricle and there is bowing of the septum pellucidum with early contralateral hydrocephalus.

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Fig. 11: Posterior fossa ependymoma in 15-month-old. (a) MRI: T2 axial, T1 sagittal. (b) Stained light micrograph of tumour tissue. A right posterior fossa mass is displayed, centered in the right ponto-cerebellar angle and with extension in the right Luschka.

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Fig. 12: Recurrent supratentorial ependymoma RELA fusion-positive in a 15-year-old. p65 +ve, L1-CAM +ve. MRI: T1WI with gadolinium, T2 axial. This is the most common type of supratentorial ependymoma in children, and not found in the posterior fossa or spinal cord. These tumours can be both grade II or III. L1CAM positivity correlates closely with the presence of RELA fusion.

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Fig. 13: Anaplastic clear cell ependymoma. (a) MRI: FLAIR coronal, T2WI axial. (b) Stained light micrograph of tumour tissue. These tumours have higher proliferative rate and a greater tendency to infiltrate surrounding brain or disseminate into cerebrospinal fluid causing drop metastases.

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Fig. 14: Myxopapillary ependymoma. (a) MRI: T2WI sagittal, T1WI sagittal with gadolinium contrast. (b) Stained light micrograph of tumour tissue.

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Fig. 15: Diffuse leptomeningeal glioneuronal tumour. (a) MRI: T1WI with gadolinium contrast sagittal head and upper spine. (b) Stained light micrograph of tumour tissue. There is diffuse nodular enhancing leptomeningeal disease in the brain and spine. Numerous cysts are evident in the posterior fossa at the parenchymal interfaces. Hydrocephalus is evident.

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Fig. 16: Multinodular and vacuolating tumour (MNVT). MRI: T2WI. Extensive subcortical signal abnormality left anterior and inferior temporal lobe.

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Conclusion

Genetic characteristics aid considerably in the accurate classification of central nervous system tumours and this is recognised in to the WHO 2016 Classification of Tumours of the Central Nervous System. The new classification will allow more accurate diagnosis, better therapeutics, and a more robust framework for future research.
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