Medulloblastoma

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Introduction

In this update of the WHO classification, medulloblastomas are classified according to molecular characteristics in addition to histopathological features. The molecular classification relates to the clustering of medulloblastomas into groups on the basis of transcriptome or methylome profiling and has been introduced because of its increasing clinical utility {1804}. A histopathological classification has also been retained, due to its clinical utility when molecular analysis is limited or not feasible.

Transcriptome profiling studies of medulloblastomas indicate that these tumours can be separated into several distinct molecular clusters {2524}, which by consensus have been distilled into four principal groups: WNT-activated medulloblastomas, SHH-activated medulloblastomas, group 3 medulloblastomas, and group 4 medulloblastomas.

Tumours in the WNT-activated and SHH-activated groups show activation of their respective cell signalling pathways. The four principal groups emerged from clustering analyses following transcriptome, microRNA, and methylome profiling, and there is excellent concordance across these platforms for the assignment of individual tumours {142,1804}. There are also significant associations between the four groups and specific genetic alterations and clinicopathological variables.

In the updated WHO classification, WNT-activated medulloblastomas (accounting for ~10% of cases) and SHH-activated medulloblastomas (~30% of cases) are listed separately from non-WNT/non-SHH tumours, which comprise group 3 tumours (~20% of cases) and group 4 tumours (~40% of cases). Group 3 and group 4 medulloblastomas are listed as provisional variants, because they are not as well separated as WNT-activated and SHH-activated medulloblastomas in molecular clustering analyses and by current clinical laboratory assays {448, 1335}.

2016 WHO classification of medulloblastomas

Medulloblastomas, genetically defined

- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and *TP53*-mutant
- Medulloblastoma, SHH-activated and *TP53*-wildtype
- Medulloblastoma, non-WNT/non-SHH
  - *Medulloblastoma, group 3*
  - *Medulloblastoma, group 4*

Medulloblastomas, histologically defined

- Medulloblastoma, classic
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large cell / anaplastic medulloblastoma

Medulloblastoma, NOS

Medulloblastoma has always been considered to be an embryonal tumour of the cerebellum. However, WNT-activated medulloblastomas are thought to arise from cells in the dorsal brain stem {831}, although not all brain stem embryonal tumours are WNT-activated medulloblastomas.

The established morphological variants of medulloblastoma (i.e. desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, and large cell or anaplastic medulloblastomas) have their own particular clinical associations {619, 1603,1626,1627}. Large cell and anaplastic medulloblastomas were listed as separate variants in the previous version of the classification, but because nearly all large cell tumours also demonstrate an anaplastic component and both variants are associated with a poor outcome, they are commonly considered for clinical purposes as being in a single combined category of large cell / anaplastic medulloblastoma {2208,2664}. This association and its designation have been recognized in the update of the classification.

The molecular and morphological variants of medulloblastoma listed in the new classification demonstrate particular relationships {631}. All true desmoplastic/nodular medulloblastomas and medulloblastomas

Table 8.01 Medulloblastoma subtypes characterized by combined genetic and histological parameters

Genetic profile	Histology	Prognosis
Medulloblastoma, WNT-activated	Classic	Low-risk tumour; classic morphology found in almost all WNT-activated tumours
	Large cell / anaplastic (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-mutant	Classic	Uncommon high-risk tumour
	Large cell / anaplastic	High-risk tumour; prevalent in children aged 7–17 years
	Desmoplastic/nodular (very rare)	Tumour of uncertain clinicopathological significance
Medulloblastoma, SHH-activated, *TP53*-wildtype	Classic	Standard-risk tumour
	Large cell / anaplastic	Tumour of uncertain clinicopathological significance
	Desmoplastic/nodular	Low-risk tumour in infants; prevalent in infants and adults
	Extensive nodularity	Low-risk tumour of infancy
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard-risk tumour
	Large cell / anaplastic	High-risk tumour
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard-risk tumour; classic morphology found in almost all group 4 tumours
	Large cell / anaplastic (rare)	Tumour of uncertain clinicopathological significance

Table 8.02 Characteristics of genetically defined medulloblastomas

	WNT-activated	SHH-activated		Non-WNT/non-SHH	
		TP53-wildtype	*TP53*-mutant	Group 3	Group 4
Predominant age(s) at presentation	Childhood	Infancy Adulthood	Childhood	Infancy Childhood	All age groups
Male-to-female ratio	1:2	1:1	1:1	2:1	3:1
Predominant pathological variant(s)	Classic	Desmoplastic/nodular	Large cell / anaplastic	Classic Large cell / anaplastic	Classic
Frequent copy number alterations	Monosomy 6	*PTCH1* deletion 10q loss	*MYCN* amplification *GLI2* amplification 17p loss	*MYC* amplification Isodicentric 17q	*MYCN* amplification Isodicentric 17q
Frequent genetic alterations	*CTNNB1* mutation *DDX3X* mutation *TP53* mutation	*PTCH1* mutation *SMO* mutation (adults) *SUFU* mutation (infants) *TERT* promoter mutation	*TP53* mutation	*PVT1-MYC* *GFI1/GFI1B* structural variants	*KDM6A* *GFI1/GFI1B* structural variants
Genes with germline mutation	*APC*	*PTCH1* *SUFU*	*TP53*		
Proposed cell of origin	Lower rhombic lip progenitor cells	Cerebellar granule neuron cell precursors of the external granule cell layer and cochlear nucleus (Neural stem cells of the subventricular zone)*		CD133+/lineage– neural stem cells (Cerebellar granule neuron cell precursors of the external granule cell layer)*	Unknown

*Parentheses indicate a less likely origin.

with extensive nodularity align with the SHH-activated molecular group. Virtually all WNT-activated tumours have classic morphology. Most large cell / anaplastic tumours belong either to the SHH-activated group or to group 3.

Integrated diagnosis

This updated classification is intended to encourage an integrated approach to diagnosis [1535]. When molecular analysis is feasible, combined data on both molecular group and morphological variant provide optimal prognostic and predictive information. This approach is further enhanced when specific genetic data are integrated into the diagnosis, e.g. by the inclusion of *TP53* gene status in the classification.

SHH-activated medulloblastomas are a heterogeneous group; a tumour with *TP53* mutation and large cell / anaplastic morphology has an abysmal prognosis, in contrast to SHH-activated and *TP53*-wildtype medulloblastomas with extensive nodularity, which have a good clinical outcome if treated appropriately [2870].

Some molecular genetic alterations currently used in the risk stratification of medulloblastomas, such as *MYC* amplification, are not included in the classification, but could nevertheless be incorporated into an integrated diagnosis that brings together molecular group, histopathological variant, and specific genetic alteration to enhance the level of diagnostic precision.

Immunohistochemical assays that work on formalin-fixed paraffin-embedded tissue and are readily available worldwide can be used to discern some genetically defined variants of medulloblastoma and genetic alterations with clinical utility [1240]. However, the updated classification does not make specific recommendations regarding the merits of the various methods for determining molecular groups or genetic alterations.

Definition

An embryonal neuroepithelial tumour arising in the cerebellum or dorsal brain stem, presenting mainly in childhood and consisting of densely packed small round undifferentiated cells with mild to moderate nuclear pleomorphism and a high mitotic count.

Medulloblastoma is the most common CNS embryonal tumour and the most common malignant tumour of childhood. It is now classified into molecular (i.e. genetic) variants as well as morphological variants, all with clinical utility. Most medulloblastomas arise in the cerebellum, but the WNT-activated variant has its origins in cells of the dorsal brain stem that are derived from the lower rhombic lip. Medulloblastoma variants show a broad range of morphological features, including neurocytic and ganglionic differentiation, and distinct biological behaviours. In making a diagnosis medulloblastoma, it is important to exclude histopathologically similar entities that arise in the posterior fossa, such as high-grade small cell gliomas, embryonal tumour with multilayered rosettes, and atypical teratoid/rhabdoid tumours.

Grading

Irrespective of their histological or genetic characterization, medulloblastomas correspond histologically to WHO grade IV.

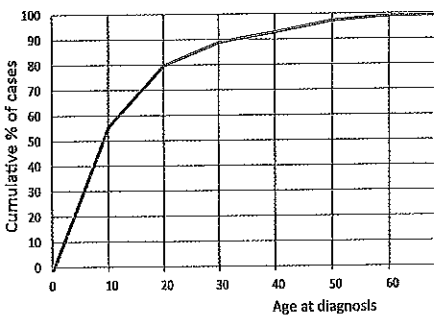

Fig. 8.01 Cumulative age distribution of medulloblastoma (both sexes), based on 831 cases (2008–2015). Data from the Brain Tumor Reference Center, Bonn.

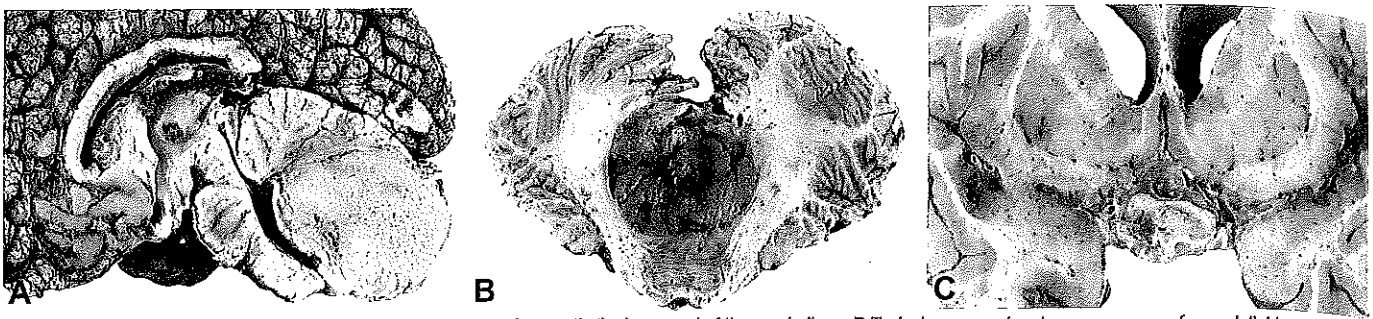

Fig. 8.02 Medulloblastoma. **A** Sagittal section. The tumour occupies mostly the lower part of the cerebellum. **B** Typical gross postmortem appearance of a medulloblastoma in the cerebellar midline, occupying the cerebellar vermis. **C** Diffuse CSF seeding by a medulloblastoma into the basal cisterns and meninges.

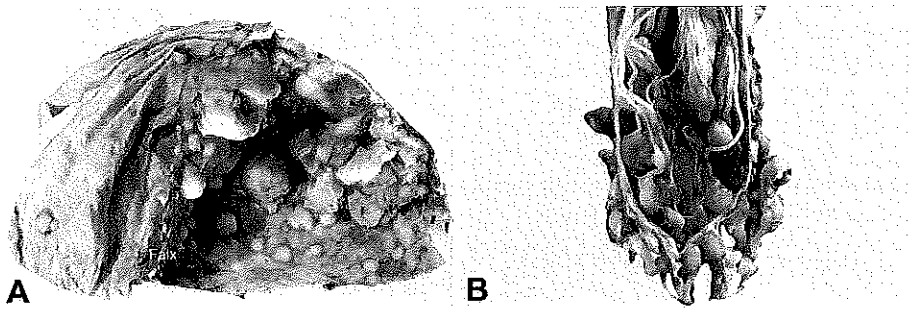

Fig. 8.03 **A** Numerous medulloblastoma metastases of various sizes on the falx cerebri and the inner surface of the dura mater covering the left cerebral hemisphere. Some smaller dural metastases are present on the contralateral side. **B** Multiple nodules in the cauda equina of the spinal cord representing CSF drop metastases of a medulloblastoma.

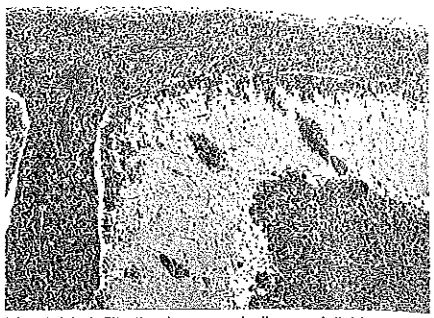

Fig. 8.04 Infiltration by a cerebellar medulloblastoma of the subarachnoid space. Note the clusters of tumour cells in the molecular layer, particularly in the subpial region.

Medulloblastoma, NOS

The diagnosis of medulloblastoma, NOS, is appropriate when an embryonal neural tumour is located in the fourth ventricle or cerebellum and the nature of biopsied tissue prevents classification of the tumour into one of the genetically or histologically defined categories of medulloblastoma. This situation usually arises when there is uncertainty about a tumour's architectural and cytological features as a result of insufficient tissue sampling or the presence of tissue artefacts. For the diagnosis of medulloblastoma, NOS, it is important to exclude histopathologically similar entities, such as high-grade small cell gliomas, embryonal tumour with multilayered rosettes, and atypical teratoid/rhabdoid tumours.

ICD-O code 9470/3

Epidemiology

Incidence

Medulloblastoma is the most common CNS embryonal tumour of childhood. Of all paediatric brain tumours, medulloblastoma is second in frequency only to pilocytic astrocytoma, and accounts for 25% of all intracranial neoplasms {673}. The annual overall incidence of medulloblastoma is 1.8 cases per 1 million population, whereas the annual childhood incidence is 6 cases per 1 million children; these incidence rates have not changed over time {1896}. As is the case with other high-grade brain tumours, the incidence of medulloblastoma differs across ethnicities. In the USA, overall annual incidence is highest among White non-Hispanics (2.2 cases per 1 million population), followed by Hispanics (2.1 per 1 million) and African Americans (1.5 per 1 million) [http://www.cbtrus.org/2011-NPCR-SEER/WEB-0407-Report-3-3-2011.pdf]. As many as a quarter of all medulloblastomas occur in adults, but < 1% of adult intracranial tumours are medulloblastomas {1645}.

Age and sex distribution

The median patient age at diagnosis of medulloblastoma is 9 years, with peaks in incidence at 3 and 7 years of age {2138}. Of all patients with medulloblastoma, 77% are aged < 19 years {673}. The tumour has an overall male-to-female ratio of 1.7:1. Among patients aged > 3 years, the male-to-female ratio is 2:1, but the incidence rates among boys and girls aged ≤ 3 years are equal {511,899}. The various molecular groups and histopathological variants of medulloblastoma have different age distributions {631, 1334,2524}.

Localization

Medulloblastomas grow into the fourth ventricle or are located in the cerebellar parenchyma {213}. Some cerebellar tumours can be laterally located in a hemisphere.

Clinical features

Medulloblastomas growing in the fourth ventricle cause increased intracranial pressure by exerting mass effect and blocking cerebrospinal fluid pathways. Therefore, most patients present with a short history of raised intracranial pressure: headaches that have increased in frequency and severity, frequent nausea upon waking, and bouts of vomiting. Cerebellar ataxia is common. Symptoms and signs relating to compression of cranial

nerves or long tracts passing through the brain stem are uncommon.

Spread

Like other embryonal tumours, medulloblastoma has a propensity to spread through cerebrospinal fluid pathways to seed the neuraxis with metastatic tumour deposits. Rarely, it spreads to organ systems outside the CNS, particularly to bones and the lymphatic system. Reports of metastasis to the peritoneum implicate ventriculoperitoneal shunts.

Macroscopy

Most medulloblastomas arise in the region of the cerebellar vermis, as pink or grey often friable masses that fill the fourth ventricle. Medulloblastomas located in the cerebellar hemispheres tend to be firm and more circumscribed, and generally correspond to the desmoplastic/nodular variant with SHH pathway activation. Small foci of necrosis can be grossly evident, but extensive necrosis is rare. In disseminated medulloblastoma, discrete tumour nodules are often found in the craniospinal leptomeninges or cerebrospinal fluid pathways.

Microscopy

Several morphological variants of medulloblastoma are recognized, alongside the classic tumour: desmoplastic/nodular medulloblastoma, medulloblastoma with extensive nodularity, and large cell / anaplastic medulloblastoma. Their specific microscopic architectural and cytological features are described in the corresponding sections of this volume. A dominant population of undifferentiated cells with a high nuclear-to-cytoplasmic ratio and mitotic figures is a common feature, justifying the designation "embryonal", but it is important to consider other entities in the differential diagnosis. High-grade small cell gliomas and some ependymomas have an embryonal-like cytology, and elements of the embryonal tumour with multilayered rosettes or atypical teratoid/rhabdoid tumour can be identical to medulloblastoma. Any of these entities can be confused with medulloblastoma, especially in small biopsies, so determining a tumour's immunophenotype or genetic profile is an important part of working through the differential diagnosis.

Two distinctive morphological variants of medulloblastoma are described in this section, because they may occur in the setting of a classic or large cell / anaplastic tumour and are no longer considered distinct histopathological variants. These are the rare (accounting for < 1% of cases) medulloblastoma with myogenic differentiation (previously called medullomyoblastoma) and medulloblastoma with melanotic differentiation (previously called melanocytic medulloblastoma). Although these tumours are very rare, it is not uncommon for their phenotypes to occur together.

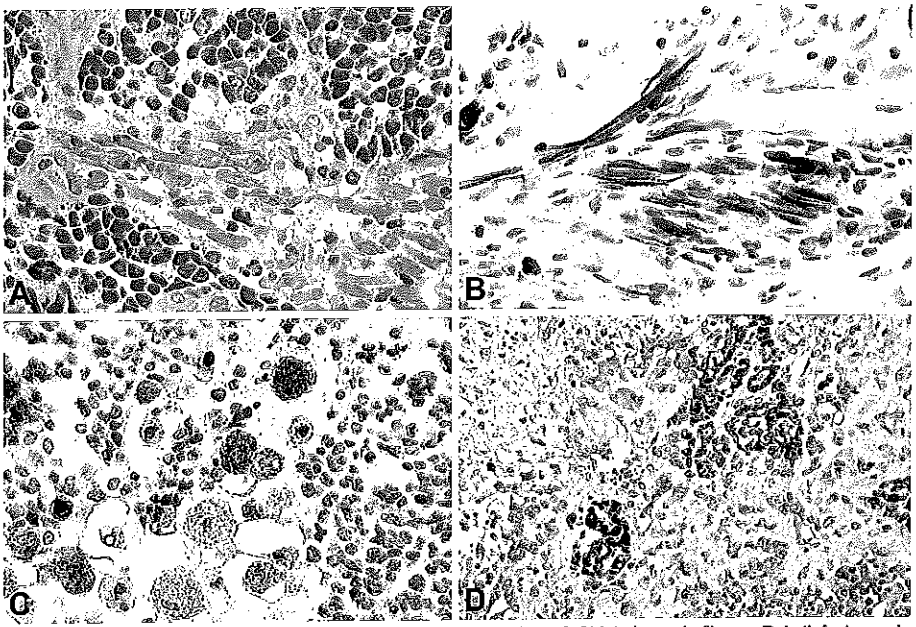

Fig. 8.05 Medulloblastoma with myogenic or melanotic differentiation. **A** Striated muscle fibres. **B** Anti–fast myosin immunostaining of highly differentiated, striated myogenic cells. **C** Biphasic pattern of small undifferentiated embryonal cells and large rhabdomyoblasts immunostaining for myoglobin. **D** Melanotic cells commonly appear as tubular epithelial structures, which are immunopositive for HMB45 and cytokeratins.

In addition to a conventional embryonal element, medulloblastoma with myogenic differentiation contains a variable number and distribution of spindle-shaped rhabdomyoblastic cells and sometimes large cells with abundant eosinophilic cytoplasm {2211,2383}. Occasionally, elongated differentiated strap cells, with the cross-striations of skeletal muscle, are evident.

Medulloblastoma with melanotic differentiation contains a small number of melanin-producing cells, which sometimes form clumps {730,1965}. These may appear entirely undifferentiated (like other embryonal cells) or have an epithelioid phenotype. Epithelioid melanin-producing cells may form tubules, papillae, or cell clusters.

Immunophenotype

Although a few medulloblastomas express no neural antigens, the expression of markers of neuronal differentiation is common. Immunoreactivity for synaptophysin, class III beta-tubulin, or NeuN is demonstrated at least focally in most medulloblastomas. Homer Wright rosettes and nodules of neurocytic differentiation are immunopositive for these markers. In contrast, expression of NFPs is rare. GFAP-immunopositive cells are often found among the undifferentiated embryonal cells of a medulloblastoma; however, they generally show the typical spider-like appearance of reactive astrocytes and tend to be more abundant near blood vessels. These cells are usually considered to be entrapped astrocytes, although the observation of similar cells in extracerebral metastatic deposits raises the possibility that at least some are well-differentiated neoplastic astrocytes. Cells showing GFAP immunoreactivity and the cytological features of bona fide neoplasia can be observed in approximately 10% of medulloblastomas. In medulloblastoma with myogenic differentiation, cells demonstrating myogenic differentiation are immunopositive for desmin or myogenin, but not alpha-SMA. In medulloblastomas with melanotic differentiation, melanin-producing cells express HMB45 or melan-A, and the clumps of epithelioid cells associated with focal melanin production generally

show immunoreactivity for cytokeratins. Nuclear SMARCB1 and SMARCA4 expression is retained in all medulloblastoma variants; the loss of expression of one of these SWI/SNF complex proteins in the context of an embryonal tumour is characteristic of atypical teratoid/rhabdoid tumour.

Genetic susceptibility

Medulloblastomas occur in the setting of several inherited cancer syndromes: naevoid basal cell carcinoma syndrome (also called Gorlin syndrome; see p. 319), Li–Fraumeni syndrome; see p. 310), mismatch repair cancer syndrome (Turcot syndrome, p. 317), Rubinstein–Taybi syndrome {249A}, and Nijmegen breakage syndrome {1058A}.

Genetic susceptibility to medulloblastoma has been documented in monozygotic twins {434}, siblings, and relatives {1065,2666}. Association with other brain tumours {673} and Wilms tumour {1846, 2062} has also been reported.

Medulloblastomas, genetically defined

Medulloblastoma, WNT-activated

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Definition

An embryonal tumour of the cerebellum / fourth ventricle composed of small uniform cells with round or oval nuclei that demonstrate activation of the WNT signalling pathway.

Nearly all WNT-activated medulloblastomas are classic tumours. WNT-activated tumours with an anaplastic morphology have been reported, but are very rare. The WNT pathway activation that is characteristic of this medulloblastoma can be demonstrated by the accumulation of beta-catenin immunoreactivity in tumour cell nuclei, but an optimal evaluation combines this method with detection of monosomy 6 or *CTNNB1* mutation; approximately 85% of WNT-activated medulloblastomas defined by immunohistochemistry or gene expression profiling demonstrate monosomy 6 and/or harbour a *CTNNB1* mutation.

WNT-activated medulloblastoma is thought to originate from the dorsal brain stem to fill the fourth ventricle. WNT-activated tumours account for approximately 10% of all medulloblastomas. Most cases present in children aged between 7 and 14 years, but they can also occur in young adults. This variant has an excellent prognosis with standard therapeutic approaches. Besides *CTNNB1*, genes that are recurrently mutated in WNT-activated medulloblastomas include *TP53*, *SMARCA4*, and *DDX3X*.

ICD-O code

9475/3

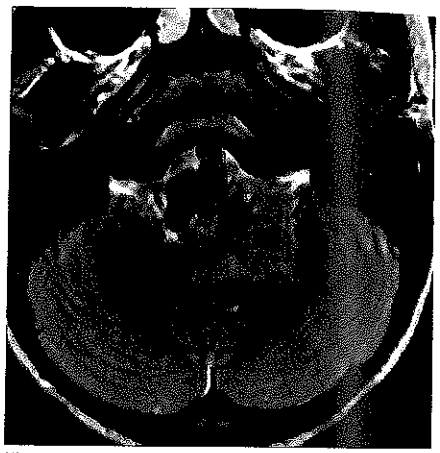

Fig. 8.06 WNT-activated medulloblastomas are usually centred on the foramen of Luschka, but tumours frequently spread along the lateral wall of the fourth ventricle and appear intraventricular.

Grading

WNT-activated medulloblastoma corresponds histologically to WHO grade IV. However, this genetically defined variant

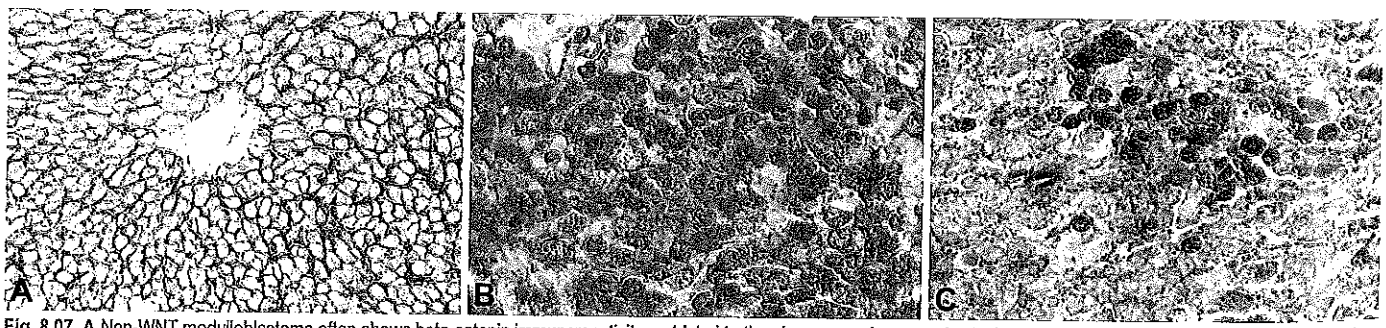

Fig. 8.07 **A** Non-WNT medulloblastoma often shows beta-catenin immunoreactivity restricted to the plasma membrane and cytoplasm. **B** WNT-activated medulloblastoma. Nuclear immunoreactivity for beta-catenin indicates activation of the WNT pathway. **C** WNT-activated medulloblastoma. Immunoreactivity for beta-catenin manifests as groups of positive nuclei in some WNT-activated medulloblastomas.

has an excellent prognosis with standard therapeutic approaches.

Epidemiology

WNT-activated tumours account for about 10% of all medulloblastomas {634,777,1972}. They typically occur in older children and also account for a significant proportion (~15%) of adult medulloblastomas, but hardly ever occur in infants.

Localization

Some reports indicate that WNT-activated medulloblastomas are all located in the cerebellar midline, with or without close contact to the brain stem {831,2534}, and one report suggests that these tumours are more precisely localized to the cerebellar peduncle or cerebellopontine angle {1936}.

Imaging

MRI of WNT-activated medulloblastomas shows tumours located in the cerebellar midline / cerebellopontine angle, with many in close contact to the brain stem {831}.

Microscopy

Nearly all WNT-activated medulloblastomas have a classic morphology; anaplastic WNT-activated tumours have been reported, but are very rare {631}. Desmoplastic/nodular medulloblastomas do not occur in this group.

Immunophenotype

WNT-activated medulloblastomas have the same neural protein immunoprofile as other classic medulloblastomas. Their growth fraction as estimated by the Ki-67 proliferation index is also the same. Nearly all medulloblastomas show some cytoplasmic immunoreactivity for beta-catenin, but WNT-activated tumours show nuclear beta-catenin immunoreactivity in most cells, although staining can be patchy in about one quarter of cases {630,631}.

Cell of origin

WNT-activated medulloblastomas are thought to arise from cells in the dorsal brain stem that originate from the lower rhombic lip {831}. The DNA methylation fingerprint of these tumours, which might be the best evidence for cell of origin in human tissues, indicates that WNT-activated medulloblastoma has a profile distinct from those of other medulloblastoma subgroups {1049,1972,2345}.

Genetic profile

A recent meta-analysis of all large next-generation sequencing datasets showed that approximately 90% of WNT-activated medulloblastomas contained somatic mutations in exon 3 of *CTNNB1* {1804}. Other recurrently mutated genes in WNT-activated medulloblastomas include *DDX3X* (in 50% of cases), *SMARCA4* (in 26.3%), *KMT2D* (in 12.5%), and *TP53* (in 12.5%). In addition to *CTNNB1* mutation, monosomy 6 has long been established as a hallmark genetic aberration in WNT-activated medulloblastomas, occurring in approximately 85% of cases {472,1334}.

Genetic susceptibility

There is a rare association between *APC* germline mutation and WNT-activated medulloblastoma {937,1057}.

Prognosis and predictive factors

The prognosis of patients with WNT-activated medulloblastoma is excellent; with current surgical approaches and adjuvant therapy regimens, overall survival is close to 100% {634,2549}. Unlike in SHH-activated medulloblastomas, *TP53* mutations in WNT-activated medulloblastomas (which are all somatic and most commonly heterozygous) do not confer a worse prognosis {2870}. Predictive biomarkers have not yet been established within the WNT-activated molecular group.

Medulloblastoma, SHH-activated

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Medulloblastoma, SHH-activated and TP53*-mutant*

Definition

An embryonal tumour of the cerebellum with evidence of SHH pathway activation and either germline or somatic TP53 *mutation.*

In large series of tumours, SHH-activated medulloblastomas tend to have similar transcriptome, methylome, and microRNA profiles. SHH pathway activation in *TP53*-mutant tumours is associated with amplification of *GLI2*, *MYCN*, or *SHH*. Mutations in *PTCH1*, *SUFU*, and *SMO* are generally absent. Large cell / anaplastic morphology and chromosome 17p loss are also common in SHH-activated and *TP53*-mutant tumours. Patterns of chromosome shattering known as chromothripsis are often present.

SHH-activated tumours account for approximately 30% of all medulloblastomas and originate from rhombic lip–derived cerebellar granule neuron precursors, the proliferation of which is dependent on SHH signalling activity. SHH-activated and *TP53*-mutant medulloblastomas are rare and generally found in children aged 4–17 years. Clinical outcomes in patients with SHH-activated and *TP53*-mutant tumours are very poor.

ICD-O code 9476/3

Medulloblastoma, SHH-activated and TP53*-wildtype*

Definition

An embryonal tumour of the cerebellum with molecular evidence of SHH pathway activation and an intact TP53 *locus.*

SHH pathway activation in *TP53*-wildtype tumours can be associated with germline or somatic mutations in the negative regulators *PTCH1* or *SUFU*, as well as activating somatic mutations in *SMO* or (rarely) amplification of *GLI2*. Desmoplastic/nodular medulloblastomas and medulloblastomas with extensive nodularity are always included in the SHH-activated group, but tumours with a hedgehog signalling pathway signature can also have a classic or large cell / anaplastic morphology, particularly in older children.

Patients with SHH-activated and *TP53*-wildtype medulloblastomas are generally children aged < 4 years, adolescents, or young adults. In addition to genetic changes activating SHH signalling, mutations in *DDX3X* or *KMT2D* and amplification of *MYCN* or *MYCL* are sometimes seen, as are deletions of chromosomal arms 9q, 10q, and 14q. Clinical outcomes in patients with SHH-activated tumours are variable.

ICD-O code 9471/3

Grading

Like all medulloblastomas, SHH-activated and *TP53*-mutant medulloblastoma and SHH-activated and *TP53*-wildtype medulloblastoma correspond histologically to WHO grade IV.

Epidemiology

SEER data from 1973–2007 suggest medulloblastoma incidence rates of 6.0 cases per 1 million children aged 1–9 years and 0.6 cases per 1 million adults aged > 19 years {2382}. SHH-activated medulloblastomas in general show a bimodal age distribution, being most common in infants and young adults, with a male-to-female ratio of approximately 1.5:1 {1804}. In contrast, SHH-activated and *TP53*-mutant tumours are generally found in children aged 4–17 years {1333}. In one study that included 133 SHH-activated medulloblastomas, 28 patients (21%) had a *TP53* mutation, and the median age of these patients was approximately 15 years {2870}.

Localization

SHH-activated medulloblastomas were proposed in one report to involve mainly the lateral cerebellum, a finding related to their origin from granule neuron precursors {831}. A subsequent study that included 17 SHH-activated medulloblastomas found that although 9 of those tumours were hemispheric, the other 8 were centred in, or significantly involved, the vermis {2534}. The localization of SHH-activated tumours may be age-dependent. A third study found that in older children and young adults, SHH-activated medulloblastomas grow predominantly in the rostral cerebellar hemispheres, whereas in infants they more frequently involve the vermis {2716}. Specific data on the localization of SHH-activated and *TP53*-mutant or *TP53*-wildtype medulloblastoma are not yet available.

Imaging

On CT and MRI, medulloblastomas present as solid, intensely contrast-enhancing masses. SHH-activated medulloblastomas are most often identified in the lateral hemispheres, but can also involve midline structures {831,2534}. Oedema was relatively common in one imaging series that included 12 desmoplastic/nodular medulloblastomas and 9 medulloblastomas with extensive nodularity {743}. A nodular, so-called grape-like pattern on MRI often characterizes medulloblastoma with extensive nodularity because of the tumour's distinctive and diffuse nodular architecture {820,1744}. Medulloblastomas involving the peripheral cerebellar hemispheres in adults occasionally present as extra-axial lesions resembling meningiomas or acoustic nerve schwannomas {154}.

Spread

Medulloblastomas have the potential to invade locally, metastasize through the cerebrospinal fluid, or (more rarely) spread outside the CNS. Overall, SHH-activated medulloblastomas are less frequently metastatic than group 3 tumours, but spread within the neuraxis is often a presenting feature of SHH-activated and *TP53*-mutant medulloblastoma. The molecular groups of medulloblastoma, including SHH-activated tumours, have been shown to remain stable in

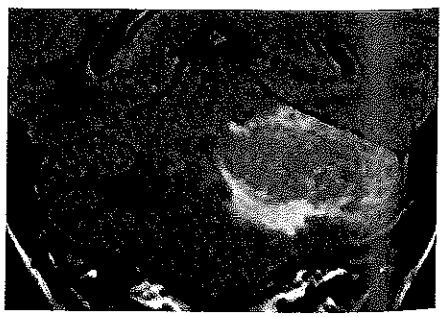

Fig. 8.08 FLAIR MRI of SHH-activated medulloblastoma. These tumours often originate from the cerebellar hemisphere.

comparisons of primary and metastatic lesions {2692}. However, *TP53* mutation can sometimes be seen in a local or distant relapse even when it is not present in the primary medulloblastoma {1003}.

Macroscopy

Some SHH-activated medulloblastomas tend to be firm and more circumscribed than other tumours, reflecting intratumoural desmoplasia. Small foci of necrosis can be grossly evident, but extensive necrosis is rare in SHH-activated tumours.

Microscopy

Desmoplastic/nodular and medulloblastoma with extensive nodularity variants of medulloblastoma are always included in the SHH-activated group, but this molecular group can also have a classic or large cell / anaplastic morphology. In one study, diffuse anaplasia was seen in 66% of all SHH-activated and *TP53*-mutant medulloblastomas, but in less than 10% of *TP53*-wildtype tumours {2870}.

Immunophenotype

Gene expression and methylation profiling remain the gold standard for defining molecular groups of medulloblastoma. However, SHH-activated medulloblastomas express a signature of activated hedgehog signalling, and several proteins have been found to be useful as surrogate markers for this activity, including GAB1 {631}, TNFRSF16 {332,1402}, and SFRP1 {1805}. One study defined a diagnostic immunohistochemical method that can distinguish between WNT-activated, SHH-activated, and non-WNT/non-SHH tumours using formalin-fixed paraffin-embedded material {631}. GAB1 and YAP1 are the immunohistochemical markers indicating SHH activation. The anti-GAB1 antibody labelled only tumours with an SHH-activated profile or *PTCH1* mutation, whereas the anti-YAP1 antibody labelled tumour cells in both WNT-activated and SHH-activated medulloblastomas, but not non-WNT/non-SHH medulloblastomas. Non-desmoplastic SHH-activated medulloblastomas generally show widespread and strong immunoreactivities for GAB1 and YAP1, whereas desmoplastic/nodular tumours display stronger staining for these proteins within internodular regions {631, 1670}.

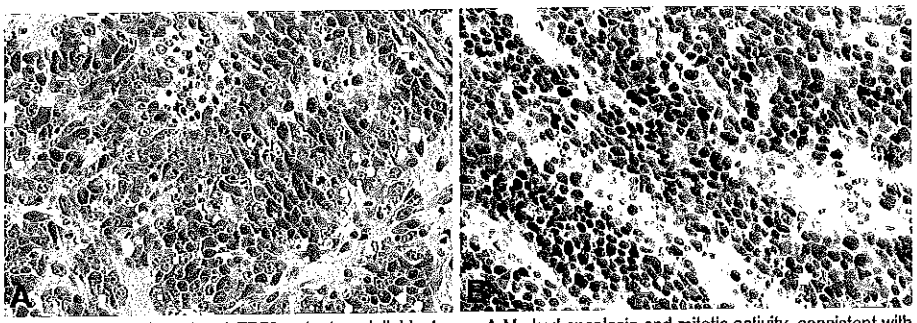

Fig. 8.09 SHH-activated and *TP53*-mutant medulloblastoma. **A** Marked anaplasia and mitotic activity, consistent with large cell / anaplastic medulloblastoma. **B** Immunoreactivity for p53, reflecting the presence of a *TP53* mutation.

Like other medulloblastomas, SHH-activated medulloblastomas can express MAP2 and synaptophysin. In SHH-activated medulloblastomas with features of medulloblastoma with extensive nodularity, strong NeuN nuclear labelling can be seen in large islands with advanced neurocytic differentiation. Pathological p53 accumulation can be detected in a small proportion of SHH-activated medulloblastomas, frequently in association with signs of cytological anaplasia. This is correlated with somatic *TP53* mutation {2482}, and can also be linked to germline *TP53* mutations (Li–Fraumeni syndrome) {2075}.

Cell of origin

SHH-activated medulloblastomas are thought to derive from ATOH1-positive cerebellar granule neuron precursors {2310,2817}. It has also been suggested that a proportion of SHH-activated medulloblastomas could arise from granule neuron precursors of the cochlear nuclei, a derivative of the auditory lower rhombic lip of the brain stem {884}. Approximately half of all patients with SHH-activated and *TP53*-mutant medulloblastoma have *TP53* mutations in the germline {2870}. This suggests that this mutation may play a key role in early transformation.

Genetic profile

Mutations and other genetic alterations activating hedgehog signalling are the main molecular drivers of SHH-activated medulloblastoma, with alterations involving known pathway genes in 116 (87%) of 133 SHH-activated tumours in a recent study {1333}. *PTCH1*, the principal gene underlying naevoid basal cell carcinoma syndrome, which predisposes patients to developing basal cell carcinoma and medulloblastoma, was mapped to 9q22 by linkage analysis. LOH in this region has also been demonstrated in many sporadic desmoplastic/nodular medulloblastomas {2296}. PTC1 is an inhibitor of hedgehog signalling and is particularly important in cerebellar development. The pathway ligand SHH is secreted by Purkinje cells and is a major mitogen for cerebellar granule cell progenitors in the external germinal layer {2715}. Activation of the pathway occurs when the SHH ligand binds to PTC1, releasing PTC1 from SMO inhibition and activating GLI transcription factors in the primary cilia {280}. The SHH pathway can thus be aberrantly activated by loss of PTC1 function or increased activity of SHH, SMO, or GLI factors.

Early array-based expression studies identified active SHH signalling in a subset of medulloblastomas, which were often desmoplastic/nodular or medulloblastomas with extensive nodularity {2000, 2549}. Larger mRNA expression profiling experiments confirmed the existence of this group, and it was adopted as one of four principal molecular groups by an international consensus panel {2524}. Analyses of genome-wide methylation profiles have also supported the existence of a distinct SHH-activated group, and can be performed in formalin-fixed tissue {1049}. Smaller sets of SHH-associated genes measured using gene counting technology or quantitative RT-PCR can also be used to define this molecular group for the purpose of clinical classification {1808, 2355}.

Structural variations or mutations in DNA are often distinct across the various medulloblastoma molecular groups. High-level amplifications associated with the SHH-activated group include loci containing *MYCL*, *GLI2*, *PPM1D*, *YAP1*, and *MDM4* {1807}. The *MYCN* locus is often amplified in both SHH-activated and group 4 medulloblastomas. Many of these altered loci have known links to the SHH pathway. *MYCN* expression is directly regulated by GLI transcription factors in both granule

cell precursors and tumours {1839}. YAP1 is also a known target and important effector of hedgehog signalling in neoplastic and non-neoplastic cerebellar progenitors {690}. Homozygous deletions at the *PTEN* and *PTCH1* loci have also been found preferentially or exclusively in SHH-activated tumours compared with other molecular groups {1807}.

Somatic mutations are relatively rare in medulloblastoma compared with other tumours, with a median of 12 non-silent and 4 silent mutations reported in one study of coding regions across 92 primary medulloblastoma/normal sample pairs {2042}. In this and a similar study {2142}, mutations in *PTCH1*, *SUFU*, and other genes associated with the hedgehog signalling pathway were found exclusively in SHH-activated tumours. However, in some SHH-activated tumours, no clear genetic explanation for SHH pathway activation can be determined.

The most common somatic point mutations are in the *TERT* promoter, resulting in increased telomerase activity. An analysis of 466 medulloblastomas revealed *TERT* mutations in 21% overall, with the highest frequency – 83% (55 of 66 cases) – identified among the adult cases of the SHH-activated group, in which they were linked to good outcomes {2098}. Point mutations in *TP53*, particularly in SHH-activated rather than WNT-activated medulloblastomas, are associated with chromothripsis, in which chromosomes shatter and acquire multiple rearrangements simultaneously in a single catastrophic event {2075}. Overall, the frequency of specific genetic changes in SHH-activated medulloblastomas seems to be somewhat different in infants, children, and adults {1333}.

Genetic susceptibility

Inherited point mutations in *TP53* in Li-Fraumeni syndrome can result in medulloblastoma, and it has been shown that these medulloblastomas belong to the SHH-activated group and are prone to chromothripsis {2075}. Patients whose SHH-activated tumours harbour *TP53* mutation or chromothripsis should be tested for germline alterations, and this high-risk group of tumours is considered a distinct variant. Mutations in *TP53* are most commonly found in the DNA binding regions encoded by exons 4 through 8 {2870}. Approximately half of all SHH-activated and *TP53*-mutant medulloblastomas have been shown to have germline rather than somatic alterations. Although some WNT-activated medulloblastomas have mutations in *TP53*, these changes have so far been somatic {2870}.

Another inherited syndrome associated with SHH-activated medulloblastoma is naevoid basal cell carcinoma syndrome (also called Gorlin syndrome). It is characterized by multiple basal cell carcinomas of the skin, odontogenic jaw keratocysts, medulloblastoma, and developmental abnormalities. Most naevoid basal cell carcinoma syndrome cases are due to heterozygous germline mutations in *PTCH1*, with mutations identified in 97 of 171 patients (56%) in one study {2376}. However, mutations in *PTCH1* and *TP53* are thought to be mutually exclusive {1333}. The age distributions of these groups also differ; medulloblastomas with germline *PTCH1* or *SUFU* mutations present in infants and children aged < 4 years, whereas those with a germline *TP53* mutation occur in older children.

Prognosis and predictive factors

SHH-activated and *TP53*-mutant medulloblastomas are associated with a very poor outcome. In one study, the 5-year overall survival of patients with an SHH-activated medulloblastoma was 76% for those with a *TP53*-wildtype tumour and 41% for those with a *TP53*-mutant tumour {2870}. Known clinical high-risk factors, such as metastatic disease, are also associated with *TP53* mutation within the SHH-activated group. It is becoming increasingly clear that some genetic prognostic markers must be interpreted within the context of molecular group. For example, although *TP53* mutations were found in 16% of WNT-activated tumours and 21% of SHH-activated tumours, they were significantly associated with a poor prognosis only in SHH-activated tumours {2870}.

Patient outcome with SHH-activated and *TP53*-wildtype medulloblastomas is varied and shows a significant association with pathological features. Medulloblastomas with extensive nodularity in infants are noted for a good prognosis, and most desmoplastic/nodular tumours in this young age group also have a relatively good outcome {2208}. The situation for SHH-activated and *TP53*-wildtype medulloblastomas with a classic or large cell / anaplastic morphology is less clear, though these appear to have a worse outcome than the two types of desmoplastic medulloblastoma, at least in infancy.

Molecular factors predicting response to therapies targeting SHH are beginning to emerge. Small-molecule inhibitors that act on the SMO receptor have been shown to be effective in some medulloblastomas with hedgehog activation, but not in other molecular groups {2143,2355}. However, SHH-activated medulloblastoma can also be resistant to SMO inhibitors, due to activation of the pathway downstream of pharmacological blockade. Such downstream activation can be present at diagnosis or can develop as a therapeutic resistance mechanism. It has been suggested that the genetic mechanism of pathway activation is linked to the likelihood of response to SMO inhibition {1333,2143}. Adults with SHH-activated medulloblastoma are more likely to harbour activating alterations in *PTCH1* or *SMO* resulting in tumours sensitive to SMO inhibitors, whereas SHH-activated medulloblastomas from infants and children (including SHH-activated and *TP53*-mutant tumours) often contain downstream alterations in *SUFU*, *GLI2*, and *MYCN* that are refractory to these pharmacological agents. It has been suggested that DNA-damaging alkylating agents and radiation should be avoided whenever possible when treating patients with a germline *TP53* mutation {2075}.

Medulloblastoma, non-WNT/non-SHH

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Definition

An embryonal tumour of the cerebellum consisting of poorly differentiated cells and excluded from the WNT-activated and SHH-activated groups by molecular testing.

Non-WNT/non-SHH medulloblastomas are either group 3 or group 4 medulloblastomas. These are classic or large cell / anaplastic tumours that cluster into two groups in terms of transcriptome, methylome, and microRNA profiles as analysed across large series of medulloblastomas. Distinct methylome profiles probably reflect a different histogenesis of the four medulloblastoma groups, although tumours from groups 3 and 4 are more similar to each other than to WNT-activated or SHH-activated medulloblastomas (see Table 8.01, p. 184).

The group 3 transcriptome profile is characterized by relatively high expression of *MYC*, and *MYC* amplification is overrepresented in this molecular group. Group 4 tumours are characterized by recurrent alterations in *KDM6A* and *SNCAIP*, as well as in other genes. Non-WNT/non-SHH tumours account for approximately 60% of all medulloblastomas and typically have classic histopathological features. Most non-WNT/non-SHH tumours present in childhood; they are relatively uncommon in infants and adults.

ICD-O code 9477/3

Epidemiology

Group 3 medulloblastomas account for approximately 20% of all cases, and for a higher proportion of cases (~45%) in infants. Group 3 medulloblastoma is exceedingly rare in adults {1334}. Group 4 medulloblastomas are the largest molecular group, accounting for about 40% of all tumours. Peak incidence occurs in patients aged 5–15 years, with lower incidence in infants and adults {1807}.

Spread

Metastatic disease is present in about 40% of group 3 tumours at the time of diagnosis, a presentation that is a particular feature of group 3 medulloblastomas in infancy {1334,1804}.

Microscopy

Most non-WNT/non-SHH medulloblastomas have a classic morphology. These tumours occasionally exhibit areas of rosette formation or a palisading pattern of tumour cell nuclei. Nodule formation can occur in the absence of desmoplasia in non-WNT/non-SHH medulloblastomas. A reticulin preparation demonstrates no strands of collagen around or between the nodules, which otherwise show neurocytic differentiation and a reduced growth fraction, in a similar manner to nodules associated with desmoplasia in desmoplastic/nodular medulloblastoma or medulloblastoma with extensive nodularity. Large cell / anaplastic tumours in the non-WNT/non-SHH molecular group generally belong to group 3.

Immunophenotype

The neural marker immunohistochemical profile of non-WNT/non-SHH medulloblastoma is the same as those of classic or large cell / anaplastic tumours in the WNT-activated or SHH-activated groups. The tumours express synaptophysin to a variable extent, and tumour cells are rarely immunopositive for GFAP. With a panel of three antibodies (to beta-catenin, GAB1, and YAP1), non-WNT/non-SHH tumours show cytoplasmic (but not nuclear) beta-catenin immunoreactivity, and the tumour cells are immunonegative for GAB1 and YAP1 {631}.

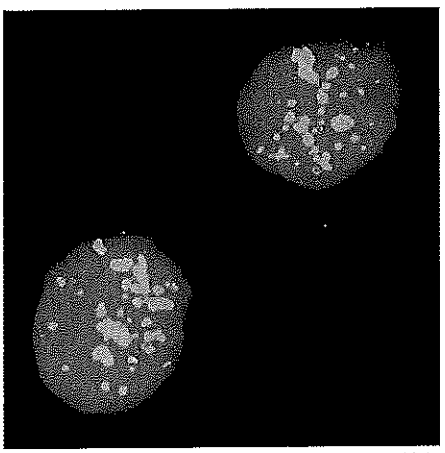

Fig. 8.10 *MYC* amplification. Nuclei show multiple clumped *MYC* signals indicative of double minutes (green). The red signals from centromeric probes indicate chromosome 8 copy number.

Genetic profile

Overexpression of *MYC* is a cardinal feature of group 3 medulloblastomas, and *MYC* amplification (often accompanied by *MYC-PVT1* fusion {1807}) is relatively common among group 3 medulloblastomas. However, *MYC* amplification is found mainly in infant disease, and occurs in < 25% of group 3 tumours overall {632, 1426}. Other recurrently mutated or focally amplified genes include *SMARCA4* (altered in 10.5% of cases), *OTX2* (in 7.7%), *CTDNEP1* (in 4.6%), *LRP1B* (in 4.6%), and *KMT2D* (in 4%) {1804}. Two recurrent oncogenes in group 3 medulloblastomas are the homologues *GFI1* and *GFI1B*, which are activated through a mechanism called enhancer hijacking {1806}. By far the most common cytogenetic aberrations in medulloblastoma (occurring in ~80% of group 4 tumours) involve copy number alterations on chromosome 17: 17p deletion, 17q gain, or a combination of these in the form of an isodicentric 17q {631,1334, 1804}. The most frequently mutated or focally amplified genes in group 4 tumours are *KDM6A* (altered in 13% of cases), the locus around *SNCAIP* (in 10.4%), *MYCN* (in 6.3%), *KMT2C* (in 5.3%), *CDK6* (in 4.7%), and *ZMYM3* (in 3.7%) {1804}. Activated GFI oncogenes have also been observed in a subset of group 3/4 tumours that do not cluster reliably into one or other group {1806}.

Prognosis and predictive factors

MYC amplification has long been established as a genetic alteration associated with poor outcome in patients with medulloblastoma {620,632,2268}. This observation is reflected in the relatively poor outcome of group 3 medulloblastomas, but *MYC* amplification has prognostic significance even among group 3 tumours {2345}. Metastatic disease at the time of presentation, which is associated with poor outcome, seems to be the most robust prognostic marker among group 4 tumours {2345}.

Medulloblastomas, histologically defined

Medulloblastoma, classic

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Giangaspero F.
Haapasalo H.
Pietsch T.
Wiestler O.D.
Pfister S.

Definition

An embryonal neuroepithelial tumour arising in the cerebellum or dorsal brain stem, consisting of densely packed small round undifferentiated cells with mild to moderate nuclear pleomorphism and a high mitotic count.

Classic medulloblastomas lack significant intratumoural desmoplasia, the marked nuclear pleomorphism of the anaplastic variant, and the cytological features of the large cell variant. Classic medulloblastomas account for 72% of all medulloblastomas. They occur throughout the patient age range of medulloblastoma, from infancy to adulthood, but predominantly in childhood, and are found in all four molecular medulloblastoma groups.

ICD-O code 9470/3

Epidemiology

The classic medulloblastoma is more frequent than its variants in childhood, but is less common than desmoplastic/nodular medulloblastoma in infants and adults.

Microscopy

Classic medulloblastomas are the archetypal CNS small blue round cell tumour. They consist of a syncytial arrangement of densely packed undifferentiated embryonal cells. Mitotic figures and apoptotic bodies are found among the tumour cells. Intratumoural desmoplasia is lacking, but pericellular desmoplasia is induced where tumour cells invade the leptomeninges. Homer Wright rosettes are found in some classic (and large cell / anaplastic) medulloblastomas.

Occasionally, nodules of neurocytic differentiation and reduced cell proliferation are evident in some areas of classic tumours, but these are never associated with internodular desmoplasia or perinodular collagen when examined in a reticulin preparation. Additionally, these non-desmoplastic nodular medulloblastomas are non-WNT/non-SHH tumours, unlike desmoplastic/nodular tumours, which belong to the SHH-activated group.

Immunophenotype

Classic medulloblastomas express various non-specific neural markers, such as NCAM1, MAP2, and neuron-specific enolase. Most cases are immunopositive for synaptophysin and NeuN, but these neuronal markers may also be absent. Immunoreactivity for NFPs is very rare. Cells showing GFAP expression and an embryonal morphology can be observed in as many as 10% of medulloblastomas {314}. When present, these cells are infrequent and tend to be scattered throughout the tumour, which is unlike the pattern of GFAP immunoreactivity in small-cell astrocytic tumours.

Nuclear SMARCB1 and SMARCA4 expression is retained in all medulloblastoma types; the loss of expression of one of these SWI/SNF complex proteins is diagnostic of atypical teratoid/rhabdoid tumour.

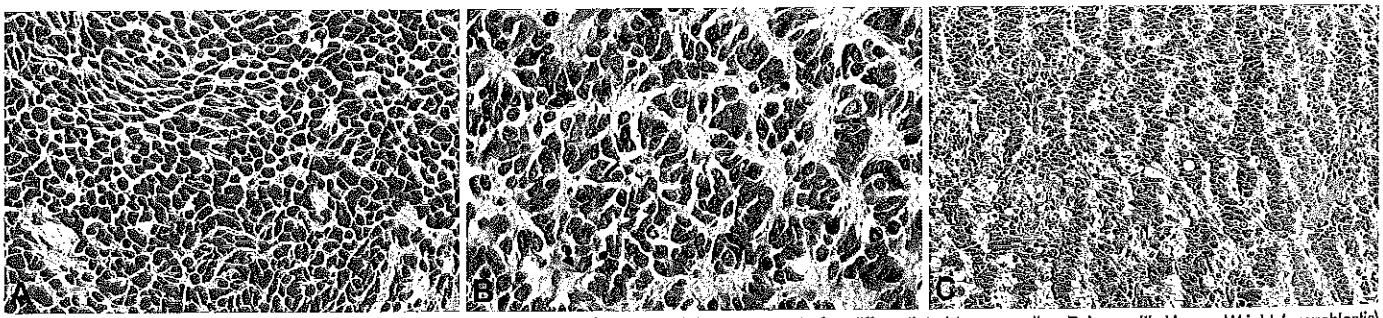

Fig. 8.11 Histopathological features of the classic medulloblastoma. **A** Typical syncytial arrangement of undifferentiated tumour cells. **B** Area with Homer Wright (neuroblastic) rosettes. **C** Arrangement of tumour cells in parallel rows (spongioblastic pattern).

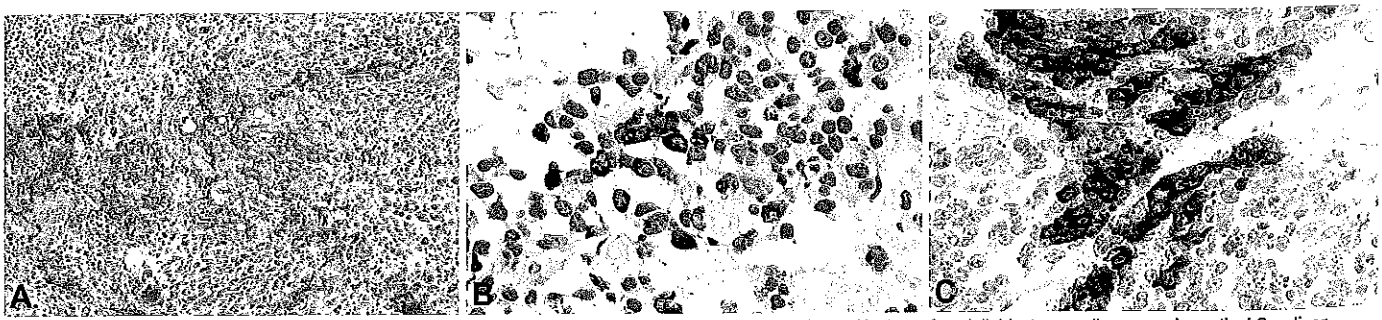

Fig. 8.12 Medulloblastoma. **A** Focal expression of synaptophysin. **B** Focal GFAP staining of tumour cells. **C** Clusters of medulloblastoma cells expressing retinal S-antigen.

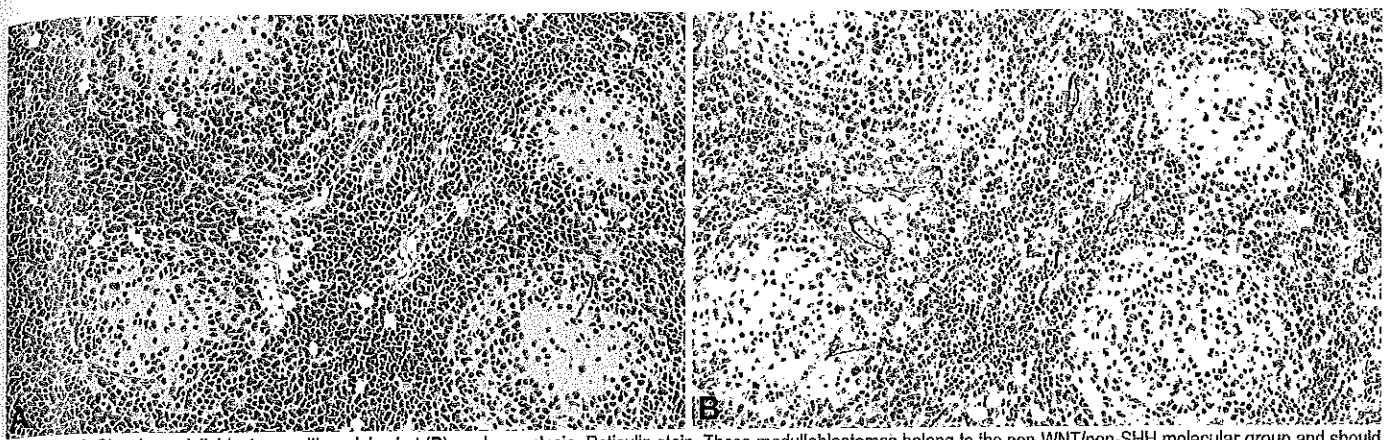

Fig. 8.13 A Classic medulloblastoma with nodules but (B) no desmoplasia. Reticulin stain. These medulloblastomas belong to the non-WNT/non-SHH molecular group and should not be confused for desmoplastic/nodular medulloblastomas.

Desmoplastic/nodular medulloblastoma

Pietsch T.
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Giangaspero F.
Wiestler O.D.
Pfister S.
Eberhart C.G.

Definition

An embryonal neural tumour arising in the cerebellum and characterized by nodular, reticulin-free zones and intervening densely packed, poorly differentiated cells that produce an intercellular network of reticulin-positive collagen fibres.

Desmoplastic/nodular medulloblastoma is characterized by specific clinical, genetic, and biological features. It occurs in the cerebellar hemispheres and the midline and has a bimodal patient age distribution, with a relatively high incidence in young children and adolescents, as well as among adults. In early childhood, it is associated with naevoid basal cell carcinoma syndrome (also called Gorlin syndrome). Desmoplastic/nodular medulloblastoma displays pathological activation of the SHH pathway, which is caused by mutations in genes that encode components of the pathway, such as *PTCH1*, *SMO*, and *SUFU*. Genetic and histological features of classic medulloblastoma, such as isochromosome 17q and neuroblastic rosettes, are absent. Desmoplastic/nodular medulloblastoma overlaps histologically with MBEN, which contains large irregular reticulin-free regions of neurocytic differentiation between narrow desmoplastic strands of proliferating embryonal cells. Desmoplastic/nodular medulloblastoma is associated with a more favourable outcome in young children than are non-desmoplastic variants of medulloblastoma.

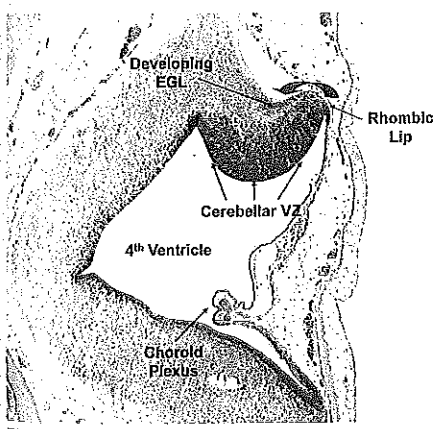

Fig. 8.14 The developing human posterior fossa. EGL, external granule layer; VZ, ventricular zone.

ICD-O code 9471/3

Grading

Like all medulloblastomas, desmoplastic/nodular medulloblastoma corresponds histologically to WHO grade IV.

Epidemiology

Desmoplastic/nodular medulloblastomas are estimated to account for 20% of all medulloblastomas {1972}. In children aged < 3 years, desmoplastic/nodular medulloblastoma accounts for 47–57% of all cases {1627,2207}. In one retrospective cohort of adult patients, desmoplastic/nodular medulloblastoma constituted 21% of all medulloblastomas {1347}.

Localization

Unlike most classic (non-WNT) medulloblastomas, which are restricted to the midline, desmoplastic/nodular medulloblastoma may arise in the cerebellar hemispheres and in the vermis. Most medulloblastomas occurring in the cerebellar hemispheres are of the desmoplastic/nodular type {332}.

Imaging

On MRI, desmoplastic/nodular medulloblastomas present as solid, frequently contrast-enhancing masses. Tumours involving the peripheral cerebellar hemispheres in adults occasionally present as extra-axial lesions.

Spread

Tumours can relapse locally, metastasize via cerebrospinal fluid pathways, and in rare cases spread to extra-CNS sites

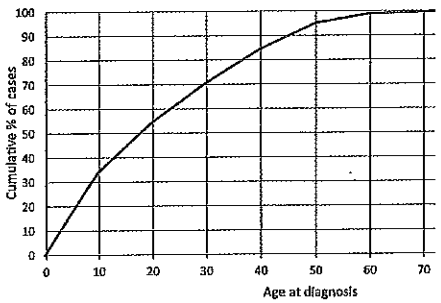

Fig. 8.15 Cumulative age distribution of 180 cases (both sexes). Data from the Brain Tumor Reference Center, Bonn.

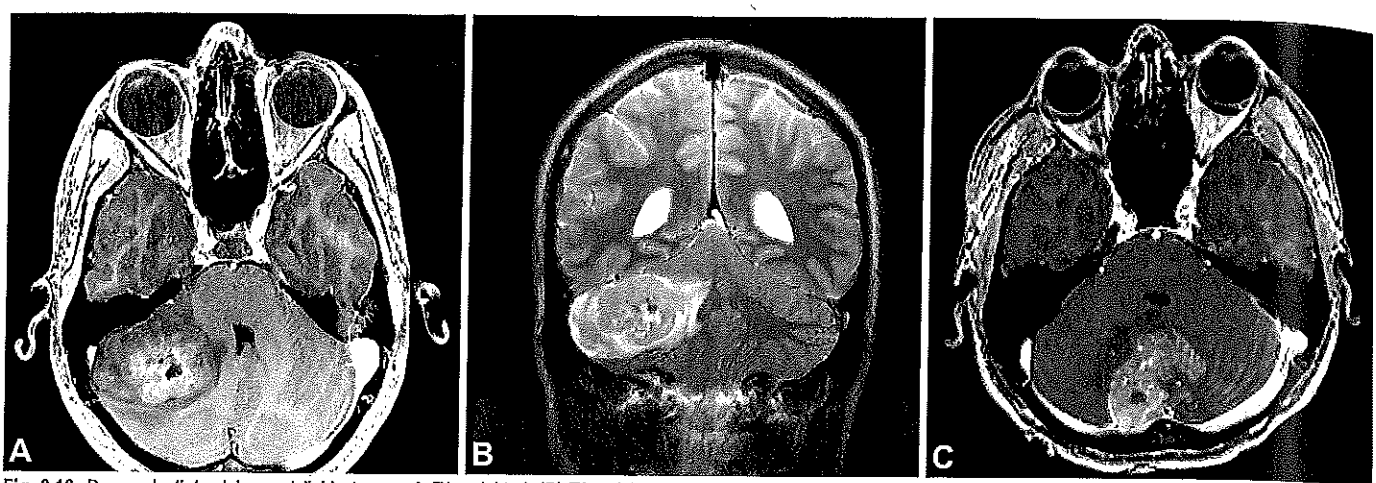

Fig. 8.16 Desmoplastic/nodular medulloblastoma. **A** T1-weighted, (B) T2-weighted contrast-enhanced MRI of tumours in the cerebellar hemisphere. **C** T1-weighted, contrast-enhanced MRI of a tumour in the vermis.

such as the skeletal system. At diagnosis, metastatic disease is found less frequently with desmoplastic/nodular medulloblastomas than with other variants.

Microscopy

Desmoplastic/nodular medulloblastoma is characterized by nodular, reticulin-free zones (so-called pale islands) surrounded by densely packed, undifferentiated, highly proliferative cells with hyperchromatic and moderately pleomorphic nuclei, which produce a dense intercellular reticulin fibre network {818, 1234}. In rare cases, this defining pattern is not present throughout the entire tumour and there is instead a more

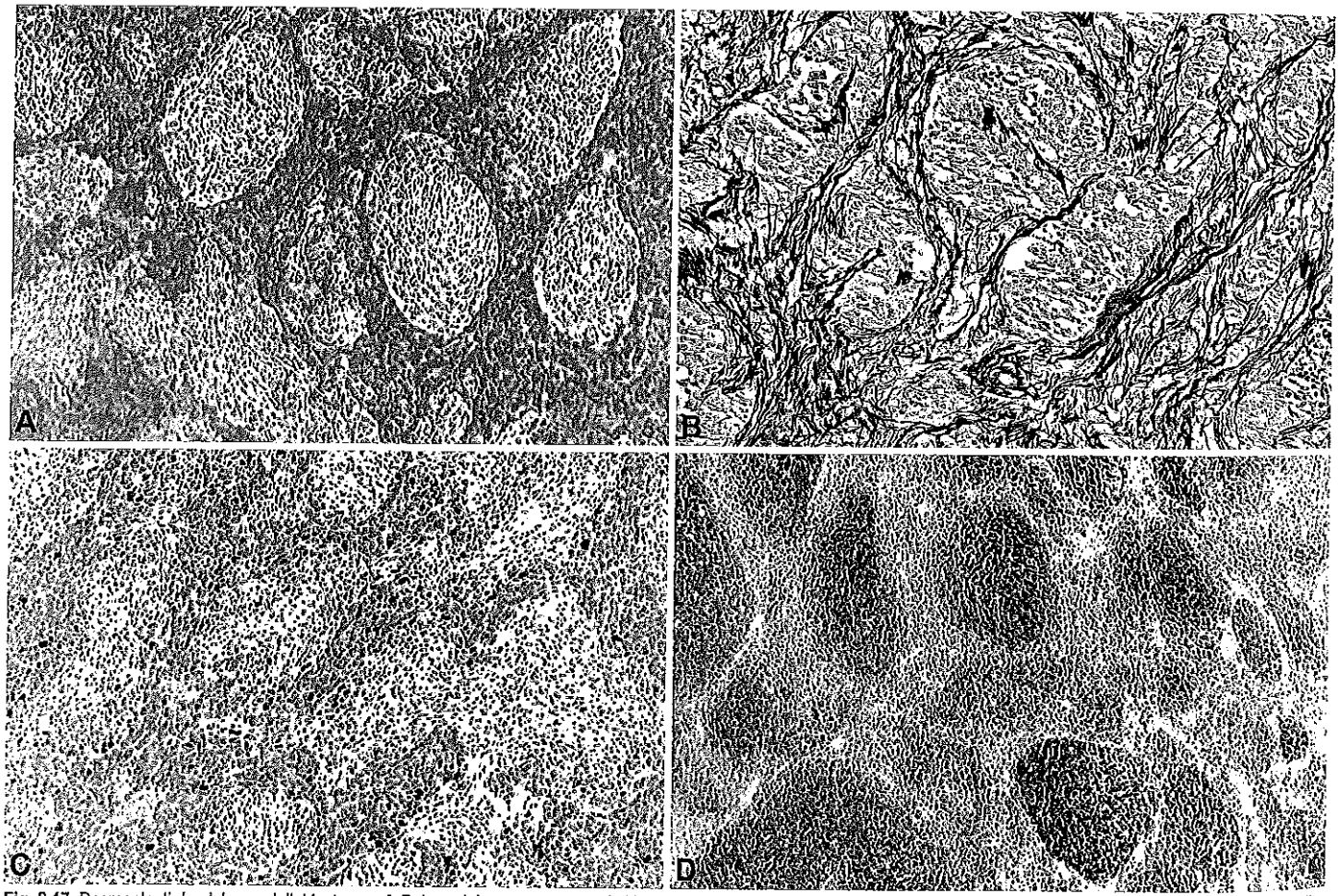

Fig. 8.17 Desmoplastic/nodular medulloblastoma. **A** Pale nodular areas surrounded by densely packed hyperchromatic cells. **B** Reticulin silver impregnation showing the reticulin-free pale islands. **C** MIB1 monoclonal antibody staining shows that the proliferative activity predominates in the highly cellular, intermodal areas. **D** Neuronal differentiation, shown by immunoreactivity for neuron-specific enolase, occurs mainly in the pale islands.

syncytial arrangement of non-desmoplastic embryonal cells present in a few areas. The nodules contain tumour cells with features of variable neurocytic maturation embedded in a neuropil-like fibrillary matrix. The level of mitotic activity in the nodules is lower than in the internodular areas. Neuroblastic rosettes are not found in desmoplastic/nodular medulloblastoma. Tumours with small nodules can easily be overlooked if no reticulin staining is performed. Medulloblastomas that show only an increased amount of reticulin fibres (without a nodular pattern) or that show a focal nodular pattern without desmoplasia are not classified as desmoplastic/nodular medulloblastoma {1627}; the two characteristic features must occur together for a diagnosis of desmoplastic/nodular medulloblastoma.

Immunophenotype

The nodules in desmoplastic/nodular medulloblastoma show variable expression of neuronal markers, including synaptophysin and NeuN. Nodules with very strong NeuN expression, which is an indicator of advanced neurocytic differentiation, are typical of medulloblastoma with extensive nodularity, but can also occur in the desmoplastic/nodular variant. The Ki-67 proliferation index is much higher in internodular areas than in nodules {1627}. Activation of the SHH pathway can be inferred by immunohistochemistry for specific targets, such as GAB1 and TNFRSF16 {631,1402}. These markers are expressed predominantly in internodular areas. GFAP expression can be found specifically in tumour cells in a subset of cases {332}. Widespread and strong nuclear accumulation of p53, suggesting a *TP53* mutation, can be detected in rare desmoplastic/nodular medulloblastomas, frequently in association with signs of cytological anaplasia. This finding can accompany either somatic or germline *TP53* alteration (Li–Fraumeni syndrome) {2075,2482}.

Cell of origin

Desmoplastic/nodular medulloblastomas are derived from granule cell progenitor cells forming the external granule cell layer during cerebellar development {332}. These progenitors are dependent on SHH (produced by Purkinje cells) as a mitogen {2715}.

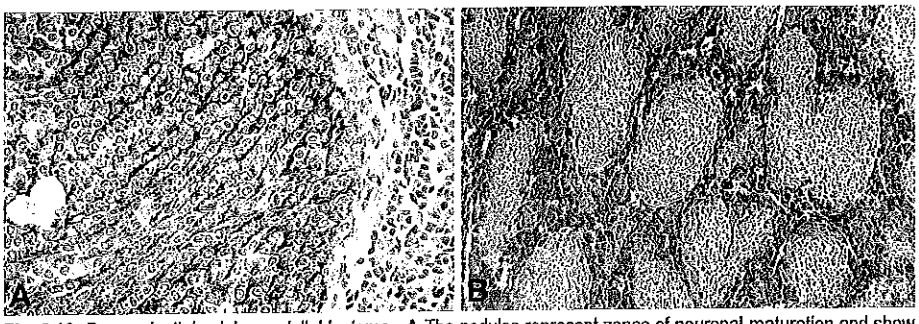

Fig. 8.18 Desmoplastic/nodular medulloblastoma. **A** The nodules represent zones of neuronal maturation and show intense immunoreactivity for synaptophysin. **B** SHH activation can be visualized by immunohistochemistry with antibodies against SHH targets, in this case, with antibodies against TNFRSF16 (also called p75-NGFR) {332,1401}, which is strongly expressed in the synaptophysin-negative internodular areas.

Genetic profile

Desmoplastic/nodular medulloblastoma displays pathological activation of the SHH pathway, which is often caused by mutations in genes encoding members of the pathway, including *PTCH1*, *SMO*, and *SUFU* {1422,1973,2523}. In a recent analysis using next-generation sequencing, 85% of desmoplastic/nodular medulloblastomas carried genetic alterations in *PTCH1*, *SUFU*, *SMO*, *SHH*, *GLI2*, or *MYCN*. This study showed a predominance of *SUFU* and *PTCH1* mutations in young children, whereas *PTCH1* and *SMO* mutations were more common in adults {1333}. Rare mutations in other genes (e.g. *LDB1*) have also been described. Recurrent *DDX3X* mutations, as well as *TERT* promoter mutations, have been identified. Allelic losses of regions on chromosomes 9q and 10q are found in some desmoplastic/nodular medulloblastomas {2296}, whereas isochromosome 17q, which is a marker of midline classic (non-WNT) and large cell / anaplastic medulloblastomas, is absent from desmoplastic/nodular medulloblastoma {1334}.

Genetic susceptibility

Naevoid basal cell carcinoma syndrome (also called Gorlin syndrome) is caused mainly by heterozygous germline mutations in *PTCH1* and rarely by germline mutations in *SUFU* or *PTCH2* {2376}. Medulloblastomas occurring in the context of naevoid basal cell carcinoma syndrome are mainly desmoplastic variants (i.e. desmoplastic/nodular medulloblastoma or medulloblastoma with extensive nodularity) {67}. It has been shown that the risk of medulloblastoma in *PTCH1*-related naevoid basal cell carcinoma syndrome is approximately 2%, and that the risk is 20 times the value in *SUFU*-related naevoid basal cell carcinoma syndrome {2376}. In children with *SUFU*-related naevoid basal cell carcinoma syndrome, brain MRI surveillance is highly recommended {2376}. Germline mutations of *SUFU* have also been described in patients with desmoplastic medulloblastomas that do not fulfil the diagnostic criteria for naevoid basal cell carcinoma syndrome {294}. The families of infants with desmoplastic medulloblastomas should be offered genetic counselling because of the high frequency of germline alterations and naevoid basal cell carcinoma syndrome {787}.

Prognosis and predictive factors

In most cases, desmoplastic/nodular medulloblastoma in early childhood has an excellent outcome with surgery and chemotherapy alone {2207}. In a meta-analysis of prognostic factors in infant medulloblastoma, progression-free or overall survival at 8 years was significantly better for desmoplastic variants than for other medulloblastomas {2208}. No survival difference between desmoplastic/nodular medulloblastoma and classic medulloblastoma was found in a European multicentre trial involving older children with standard-risk medulloblastoma {1431}.

Medulloblastoma with extensive nodularity

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Definition

An embryonal tumour of the cerebellum characterized by many large reticulin-free nodules of neurocytic cells against a neuropil-like matrix and by narrow internodular strands of poorly differentiated tumour cells in a desmoplastic matrix.

In the medulloblastoma with extensive nodularity (MBEN), the internodular reticulin-rich component with embryonal cells is a minor element. This variant occurs predominantly in infants and is associated with a favourable outcome with current treatment regimens.

MBEN is closely related to desmoplastic/nodular medulloblastoma, with which it overlaps histopathologically and genetically; both variants are SHH-activated tumours. MBEN is associated with naevoid basal cell carcinoma syndrome (also called Gorlin syndrome).

ICD-O code

9471/3

Grading

Like all medulloblastomas, MBEN corresponds histologically to WHO grade IV.

Epidemiology

In large series, medulloblastomas with extensive nodularity account for 3.2–4.2% of all medulloblastoma variants overall {619,1972}, but in children aged < 3 years (in whom desmoplastic/nodular medulloblastomas account for as many as 50% of cases {1627,2207}), medulloblastoma with extensive nodularity has been reported to account for 20% of all cases {787}.

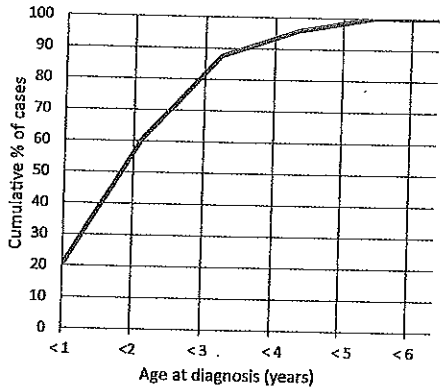

Fig. 8.19 Cumulative age distribution of 24 cases (both sexes). Data from the Brain Tumor Reference Center, Bonn.

Localization

More than 80% of medulloblastomas with extensive nodularity are located in the vermis {787}. This localization contrasts with that of desmoplastic/nodular medulloblastoma, which more frequently involves the cerebellar hemispheres.

Imaging

On MRI, medulloblastoma with exten nodularity presents as a very large m nodular lesion with enhancing grape- structures involving the vermis and so times the cerebellar hemispheres {28 Rare cases have a peculiar gyriform p sentation, in which the cerebellar folia well-delineated and enlarged, with c trast enhancement {25,787}. Downw herniation of the cerebellar tonsils a effacement of the cisternal spaces of posterior fossa can be observed.

Spread

Medulloblastoma with extensive no larity can relapse locally or (rarely) c metastasize via cerebrospinal fluid pa ways. However, such cases seem to spond well to subsequent treatment a have a favourable prognosis {820,220

Microscopy

Medulloblastoma with extensive nodul ity differs from the related desmoplast nodular variant in that is has an expand lobular architecture due to the fact th the reticulin-free zones become unus ally enlarged and rich in neuropil-like t sue. These zones contain a population small cells with round nuclei, which sho neurocytic differentiation and exhibit streaming pattern. Mitotic activity is lo or absent in these neurocytic areas. Th internodular component is markedly r duced in some areas {820,1627,245 After radiotherapy and/or chemothe apy, medulloblastomas with extensiv nodularity occasionally undergo furth

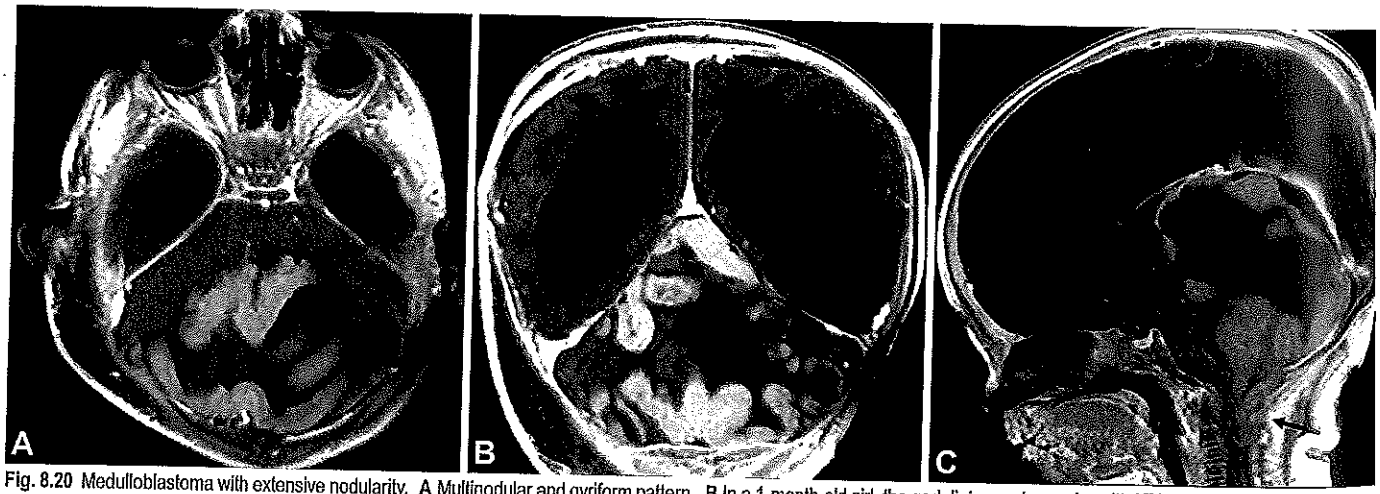

Fig. 8.20 Medulloblastoma with extensive nodularity. **A** Multinodular and gyriform pattern. **B** In a 1-month-old girl, the gadolinium-enhanced sagittal T1-weighted MRI shows a hug lesion involving both cerebellar hemispheres and the vermis. The lesion has a multinodular and gyriform pattern of enhancement. **C** Note the downward herniation of the tumou through the foramen magnum (arrow) and the marked effacement of the cisternal spaces of the posterior fossa. There is also supratentorial hydrocephalus and macrocrania.

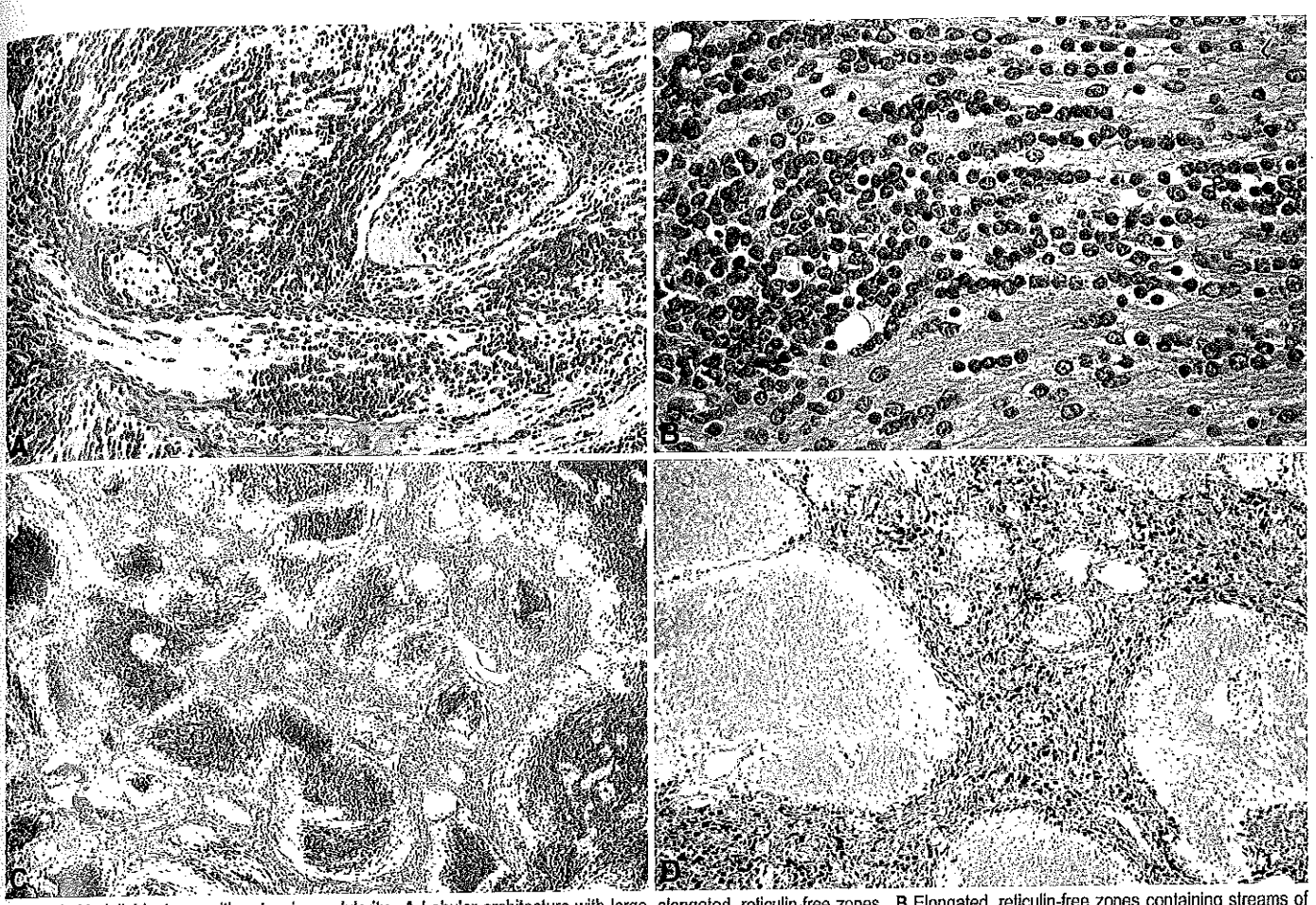

Fig. 8.21 Medulloblastoma with extensive nodularity. **A** Lobular architecture with large, elongated, reticulin-free zones. **B** Elongated, reticulin-free zones containing streams of small round neurocytic cells on a fibrillary background. **C** Strong immunoreactivity for NeuN in neurocytic cells of pale islands. **D** High MIB1 immunolabelling in internodular regions, contrasting with minimal proliferation in pale islands.

maturation into tumours dominated by ganglion cells {419,538}.

Immunophenotype

Like in desmoplastic/nodular medulloblastomas, the neuropil-like tissue and the differentiated neurocytic cells within nodules are strongly immunoreactive for synaptophysin and NeuN and the Ki-67 proliferation index is much higher in internodular areas {1627}. Activation of the SHH pathway can be demonstrated by immunohistochemistry for specific targets such as GAB1 {631} or TNFRSF16 {1402}.

Cell of origin

Medulloblastoma with extensive nodularity, like most SHH-activated medulloblastomas, seems to be derived from ATOH1-positive cerebellar granule neuron precursors {2310,2817}.

Genetic profile

Medulloblastoma with extensive nodularity carries mutations in genes encoding members of the SHH pathway. Most cases harbour a *SUFU* mutation {294}. However, a recent study of 4 medulloblastomas with extensive nodularity found a *PTCH1* mutation in 2 of the tumours and an *SUFU* and *SMO* mutation in one each of the other 2 tumours {1333}.

Genetic susceptibility

In the majority of cases, naevoid basal cell carcinoma syndrome is caused by germline mutations of *PTCH1*. In a few cases, germline mutations instead occur in *SUFU* {2376} or *PTCH2* {667,747}. Naevoid basal cell carcinoma syndrome is diagnosed in 5.8% of all patients with medulloblastoma, but in 22.7% of patients with a desmoplastic/nodular tumour variant and 41% of patients with medulloblastoma with extensive nodularity. The risk of medulloblastoma in *PTCH1*-related naevoid basal cell carcinoma syndrome is approximately 2%, and the risk is 20 times the value in *SUFU*-related naevoid basal cell carcinoma syndrome {294,1333}. In children with *SUFU*-related naevoid basal cell carcinoma syndrome, neuroimaging surveillance is recommended {2376}. Families with children that present with MBEN should be offered genetic counselling because of the high frequency of naevoid basal cell carcinoma syndrome {787,2376}.

Prognosis and predictive factors

Medulloblastoma with extensive nodularity has an excellent outcome in the majority of cases {787,1603,2208}. In an international meta-analysis of survival and prognostic factors in infant medulloblastoma, the progression-free and overall survival rates of 21 cases of medulloblastoma with extensive nodularity at 8 years were 86% and 95%, respectively {2208}. Metastatic disease at presentation did not affect the favourable prognosis, suggesting that a diagnosis of medulloblastoma with extensive nodularity confers a better outcome regardless of adverse clinical features {2208}.