

Pediatric medulloblastomas: Classification, therapeutics, and management

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Abstract

Medulloblastomas are a type of primary malignant brain tumour arising within the cerebellum and posterior cranial fossa adjacent to the fourth ventricle. Medulloblastomas are the most common primary malignant brain tumours in the pediatric population, and an increasing body of basic and clinical research is providing important insights into the etiology, pathogenesis, and development of novel therapeutics to treat these highly invasive tumours. Recent advances in genomics and transcriptomics have allowed researchers to classify and diagnose medulloblastomas based on differences in genetic and transcriptomic factors. Based on these findings, medulloblastomas have been classified into four main subgroups: 1) the Wntless/int subgroup, 2) the Sonic hedgehog subgroup, 3) Group 3 tumours, and 4) Group 4 tumours. These advancements in classifying and diagnosing medulloblastomas are significant, as different tumour subgroups have different pathophysiology, differing prognoses, and variable responses to treatment. This article will briefly highlight the latest classification criteria of pediatric medulloblastoma, review molecular and genetic features believed to be involved in the pathogenesis of each of the four subgroups of medulloblastoma, and provide an overview of treatments and therapies that are currently available and in development for medulloblastoma.

Introduction

Medulloblastomas are the most common primary malignant pediatric brain tumours that typically arise within the cerebellum, and it is estimated that 25% of medulloblastomas are derived from cerebellar granule cell precursors following inappropriate activation of the Sonic hedgehog (Shh) pathway (Figure 1).¹⁻⁴ Medulloblastomas are a heterogeneous group of clinically and molecularly diverse tumours, and are classified into four tumour subgroups based on demographic, clinical, transcriptional, and genetic characteristics.^{5,6}

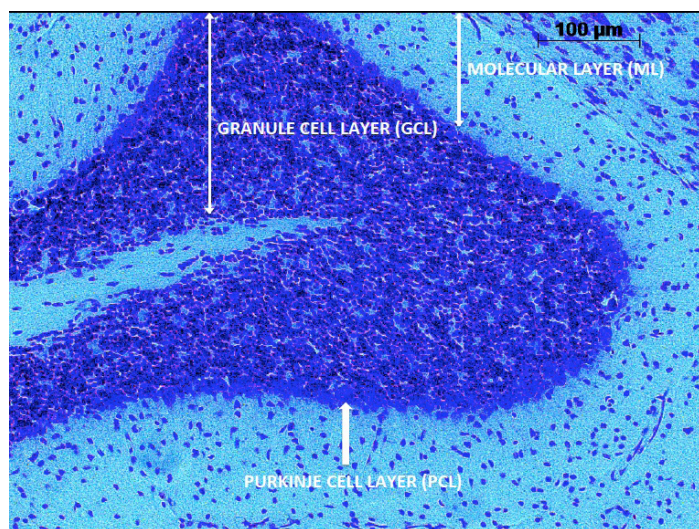


Figure 1 | Histological appearance of the cerebellar cortex in the mammalian brain. The outermost layer of the cerebellar cortex is the molecular layer (ML), which has a sparse population of neurons. The middle layer of the cerebellar cortex is the Purkinje cell layer (PCL), a monolayer of cells made up of Purkinje neurons, which constitute the sole efferent outputs of the cerebellar cortex to the rest of the central nervous system (CNS). The innermost layer of the cerebellar cortex is the densely packed granule cell layer (GCL). Approximately one-quarter of medulloblastomas arise from granule cell precursors in the cerebellum, and tumour initiation is related to the aberrant activation of the Sonic hedgehog (Shh) signaling pathway. This light photomicrograph was taken at 20x magnification using cresyl violet (CV) staining to reveal the cytoarchitecture of the cerebellar cortex.

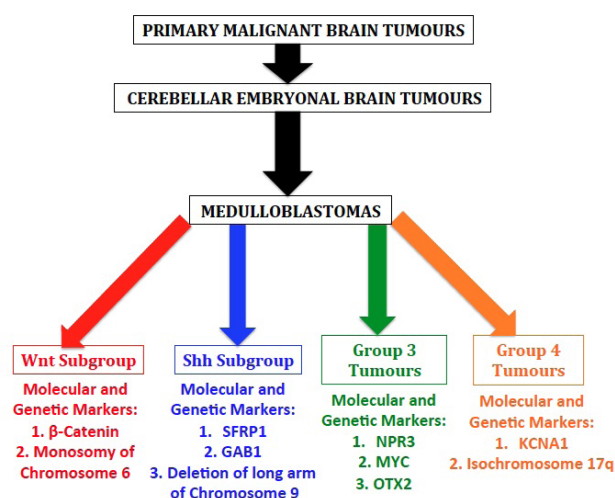


Figure 2 | Classification of cerebellar embryonal brain tumours. Medulloblastomas are classified into four main subgroups based on the molecular and transcriptomic characteristics of the tumour.

The four subgroups are: 1) the Wntless/int (Wnt) subgroup, 2) the Shh subgroup, 3) Group 3, and 4) Group 4 medulloblastomas (Figure 2).⁷ Previously, medulloblastomas were classified based on their histopathological features, and included variants such as desmoplastic/nodular, medulloblastoma with extensive nodularity, classic medulloblastoma, large cell medulloblastoma, and anaplastic medulloblastoma.⁷ Recently, several research groups have begun to classify medulloblastomas based on transcriptomic differences.⁸ These developments led to a conference being organized in 2010 where a consensus statement was created declaring that there are four main subgroups of medulloblastomas, with each subgroup subdivided into different subtypes of tumours based on the transcriptional and molecular profile of the tumour. Group 3 and Group 4 tumours are generically named because less is known about these neoplasms, though it is believed that non-Wnt and non-Shh signaling pathways are involved in the development and progression of these tumour subtypes.⁷ Here we will review the classification of the four subgroups

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of medulloblastoma and provide an overview of therapeutic options available for the treatment and management of medulloblastomas.

Wnt subgroup of medulloblastomas

The Wnt subgroup of medulloblastomas has a relatively good prognosis, with long-term survival rates estimated to be >90%; mortality in this subgroup is believed to be related to complications of therapy or due to secondary neoplasms.⁹ Genetic mutations implicated in Wnt tumours include germline mutations of the adenomatous polyposis coli gene, a Wnt signaling pathway inhibitor.¹⁰ Somatic mutations in the catenin beta-1 (*CTNNB1*) gene, which encodes β -catenin, have also been discovered in cases of sporadic medulloblastomas.¹⁰ Along with the unique genetic and transcriptomic features of Wnt tumours, this subgroup of medulloblastoma has characteristic histological features that aid in its diagnosis. A common histological feature of Wnt tumours is nuclear β -catenin staining, and this is commonly associated with *CTNNB1* mutations and monosomy of chromosome 6.¹¹ Under normal conditions, β -catenin is located in the cytoplasm and is phosphorylated by glycogen synthase kinase-3 β (GSK-3 β), leading to degradation by the ubiquitin-proteasome system.¹² With aberrant Wnt signaling, β -catenin is not phosphorylated by GSK-3 β and β -catenin is translocated to the nucleus where it acts as a transcription cofactor in the expression of genes involved in cell growth and proliferation.¹² Wnt signaling pathway mutations have been discovered in Shh and Group 3 tumours, suggesting that the Wnt pathway may be involved in the pathogenesis of multiple subgroups of medulloblastoma.¹¹ Overall, medulloblastomas are more common in males, but the Wnt subgroup of medulloblastoma affects an equal number of males and females.⁷ Wnt tumours are uncommon in infants, but can affect older children of all ages.⁷ It is hypothesized that Wnt tumours are derived from the inferior rhombic lip of the cerebellum, but further research is needed to better understand the pathogenesis of this subgroup of medulloblastoma.⁷

Shh subgroup of medulloblastomas

Shh has been implicated in tumour initiation and progression, and Shh tumours can be characterized by unique patterns of genetic mutations and transcriptome profiles. The prognosis of Shh medulloblastoma is approximately the same as Group 4 medulloblastoma; both have worse prognoses than Wnt medulloblastoma and better prognoses than Group 3 medulloblastoma.⁷ Germline mutations in the Patched 1 (*PTCH1*) gene encoding protein patched homolog 1, the Shh receptor, have been linked to Gorlin syndrome, and these mutations are associated with an increased risk of developing medulloblastoma.¹³ Mutations in the suppressor of fused homolog (*SUFU*) gene, which is an inhibitor of Shh signaling, predispose individuals to developing infantile medulloblastoma.^{14,15} Somatic mutations in the *PTCH1*, *SUFU*, and smoothened (*SMO*) genes, and gene amplifications in the glioma-associated oncogenes *GLI1* and *GLI2*, have been found in cases of sporadic medulloblastomas.^{16,17} Diagnostic features of Shh tumours can include secreted frizzled-related protein 1 or GRB2-associated-binding protein 1 immunoreactivity in histological sections. Fluorescent in situ hybridization identification of deletions of the long arm of chromosome 9 can also aid in the diagnosis of Shh tumours, which is significant because the gene encoding the Shh receptor and tumour suppressor *PTCH1* is located at chromosome 9q22.^{11,18} Shh medulloblastomas affect males and females equally; they have the highest incidence in children aged zero to three years and in young adults older than 16 years.⁷

Group 3 medulloblastomas

Diagnostic features of Group 3 medulloblastomas include immunoreactivity for natriuretic peptide receptor C in histological sections, increased expression and gene amplification of the oncogene *MYC*, and increased expression of the medulloblastoma oncogene orthodenticle homeobox 2.^{19,20} Group 3 tumours are characterized by chromosomal abnormalities such as duplication of the long arm of chromosome 1 and/or deletion of the long arms of chromosomes 5 and 10.⁷ Group 3 medulloblastoma is more common in males, can develop in both infants and older children but rarely in adults, and is frequently metastatic.⁷ Two subtypes of Group 3 tumours are Group 3 α and Group 3 β medulloblastoma. Group 3 α medulloblastoma patients have *MYC* gene amplifications, higher recurrence rates, and increased mortality as compared to other types of medulloblastoma, whereas Group 3 β medulloblastoma patients do not have *MYC* gene amplifications and have better prognoses.^{7,21}

Group 4 medulloblastomas

Group 4 medulloblastomas are diagnosed through their transcriptome profiles and tend to have a cluster of shared characteristics. Group 4 tumours have a prognosis similar to Shh medulloblastomas. The pathogenesis of Group 4 medulloblastoma is poorly understood, although potassium voltage-gated channel subfamily A member 1 is a putative immunohistochemical marker of Group 4 tumours.²¹ Chromosomal abnormalities are relatively common in Group 4 medulloblastoma, with a defect known as isochromosome 17q observed in two-thirds of Group 4 tumours.⁷ Isochromosome 17q is produced by the transverse splitting of a centromere so that both arms of the chromosome on the same side of the centromere are identical in length and possess identical genes. Isochromosome 17q is not unique to Group 4 tumours, and is also observed in 26% of Group 3 medulloblastomas.²² Group 4 medulloblastoma is more common in males, with a gender ratio of two males to one female, and 80% of females diagnosed with Group 4 medulloblastoma have X chromosome loss in tumour cells.⁷

Treatment and management of pediatric medulloblastomas

Medulloblastoma can have poor outcomes in some pediatric patients, and prognosis can vary depending on molecular, genetic, clinical, and demographic factors. Approximately one-third of medulloblastomas are diagnosed in children aged zero to three years and, compared to older children with medulloblastoma, the prognosis in younger children is worse following treatment with surgery, chemotherapy, and/or radiotherapy.^{23,24} Poorer outcomes in pediatric patients are related to metastases of the primary tumour at or after the time of diagnosis.^{25,26} The molecular and genetic subgroup of the tumour is significant, as certain types of medulloblastoma are associated with higher recurrence rates and lower long-term survival rates.^{25,26}

There are numerous side effects of treatments observed in patients. The brain is still undergoing rapid maturation, growth, and development throughout childhood. Radiotherapy and chemotherapy can have profound effects on brain structure and function. The developing brain is particularly vulnerable to post-operative radiotherapy, which can lead to significant cognitive deficits; however, in a clinical trial exploring the outcomes of post-operative chemotherapy, it was found that children with medulloblastoma treated with chemotherapy alone still had lower cognitive scores as compared to age-matched healthy controls.²⁷⁻²⁹

To reduce the neurocognitive effects of post-surgical craniospinal

irradiation (CSI), it was shown that adjuvant chemotherapy can be combined with lower radiation dose CSI to achieve the same long-term outcomes as higher radiation dose CSI treatment in standard-risk patients.³⁰⁻³² Children aged three to seven years with medulloblastoma are at the highest risk of neurocognitive deficits following CSI, and clinical trials have found that children receiving increased doses of CSI had increased intellectual decline as compared to patients receiving lower doses of CSI with or without chemotherapy.³⁰⁻³²

Previous estimates in the 1990s for patient survival following post-surgical chemotherapy with or without concurrent radiotherapy were poor, with survival rates estimated at 25-45%; however, modern multi-modal therapy in the last five years has improved survival rates to 80-85% in standard-risk medulloblastoma patients and 70% in high-risk patients.³⁰⁻³³ Improved survival rates are attributed to patients being treated and managed by following clinical risk stratification guidelines, which are based on the extent of tumour resection during neurosurgery and the presence or absence of metastatic disease.³¹

Pediatric patients greater than three years old with surgical resection resulting in <1.5 cm² of residual tumour and without metastasis are classified as standard-risk patients, with all other patients being classified as high-risk.³¹ Following surgical resection of the neoplasm, empirically based CSI with concurrent weekly vincristine and adjuvant chemotherapy following radiotherapy with agents like lomustine, cisplatin, and vincristine have become the standard of care for medulloblastoma.³⁰ Clinical trials looking at the effectiveness of treatments have noted that improvements in survival outcomes are due to improved application of empirically-based CSI and adjuvant chemotherapy following tumour resection.³⁰ In high-risk patients, empirically-based treatments have also significantly improved survival outcomes, and current surgical, CSI, and chemotherapy interventions are not strictly based on medulloblastoma subgroup.³⁰ However, the poor prognosis associated with some types of medulloblastoma following standard treatments highlights the need to identify novel therapeutic targets in different subgroups of medulloblastomas. There is also a need to develop therapies with fewer side effects and better safety profiles for treatment of brain tumours in pediatric populations.

Future directions in medulloblastoma treatment

A study published in Cell developed a high-throughput screening assay to identify putative compounds and drugs that may be useful in treating Group 3 medulloblastomas, which are associated with higher recurrence rates and increased mortality.³⁴ The study found that combination therapy of pemetrexed and gemcitabine inhibited Group 3 tumour cell growth *in vitro*, and preferentially inhibited neoplasm proliferation *in vivo* in mouse models of Group 3 medulloblastomas.³⁴ The authors noted that combination therapy of gemcitabine and pemetrexed, but not treatment with either drug alone, increased survival rates in mouse models of Group 3 tumours overexpressing the oncogene *MYC*.³⁴ This study highlights that combination therapy for medulloblastoma may be more effective than monotherapy. Treatments should be tailored to an individual patient's tumour subgroup, because there is considerable variability in prognosis and response to treatment in different types of medulloblastoma.

A recent systematic review looked at the effectiveness, safety profiles, and survival outcomes associated with classical chemotherapeutic agents and novel treatments developed for medulloblastoma. The study found that temozolomide, either taken on its own or in combination with irinotecan, showed promising

results in a large pediatric population with a more tolerable toxicity profile.^{35,36} Temozolomide also had positive synergistic effects when combined with classical chemotherapy agents or newer targeted drugs in the treatment of medulloblastomas, although the authors noted that the follow-up time for disease-free survival was short.^{35,36} Because aberrant Shh pathway activation is associated with initiation of tumour development in a number of medulloblastomas, researchers have developed targeted therapies against SMO, which is a member of the Shh signaling cascade.³⁷ The SMO inhibitor vismodegib has shown potent albeit short-lived effectiveness in the treatment of Shh tumours, and is being evaluated in a clinical trial for maintenance therapy following chemotherapy and radiotherapy in skeletally mature children with standard-risk Shh subgroup medulloblastoma.³⁸

The promising findings surrounding novel treatments targeting specific medulloblastoma subgroups will help to guide and inform future clinical treatment and management decisions. Studies examining molecular and genetic features unique to different medulloblastoma subgroups have also identified common molecular features found in all subgroups of medulloblastoma.³¹ Mutations in chromatin-modifying genes are found in all four subgroups of medulloblastoma and are also guiding the development of future medulloblastoma treatments.³¹ Demethylating agents (decitabine and azacitidine) and histone deacetylase inhibitors (vorinostat and panobinostat) are currently under investigation for the treatment of medulloblastoma.³¹

Conclusion

As with other healthcare decisions, patient and family values and preferences should be considered when developing a treatment and management plan for medulloblastoma. Patient quality of life should be taken into account as well, as treatments for medulloblastoma can be invasive. Chemotherapy and radiotherapy can produce long-lasting cognitive deficits in pediatric patients, with a subset of medulloblastoma patients at increased risk of developing leukoencephalopathy due to the toxicity of drugs like methotrexate.^{39,40}

Improved prognoses in standard-risk and high-risk medulloblastomas have come from refinements of current therapies. For example, maximal surgical resection of the tumour followed by targeted CSI and four courses of cyclophosphamide-based chemotherapy with hematopoietic stem cell therapy has improved five-year event-free survival to 70% in high-risk medulloblastoma patients.³⁰ Targeted subgroup-specific therapies should allow physicians to improve the prognosis of certain tumour subtypes, as previous pre-clinical and clinical trials have demonstrated the utility of combined multi-modal approaches in improving survival outcomes in medulloblastoma.

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