Cancer Association of South Africa (CANSA)

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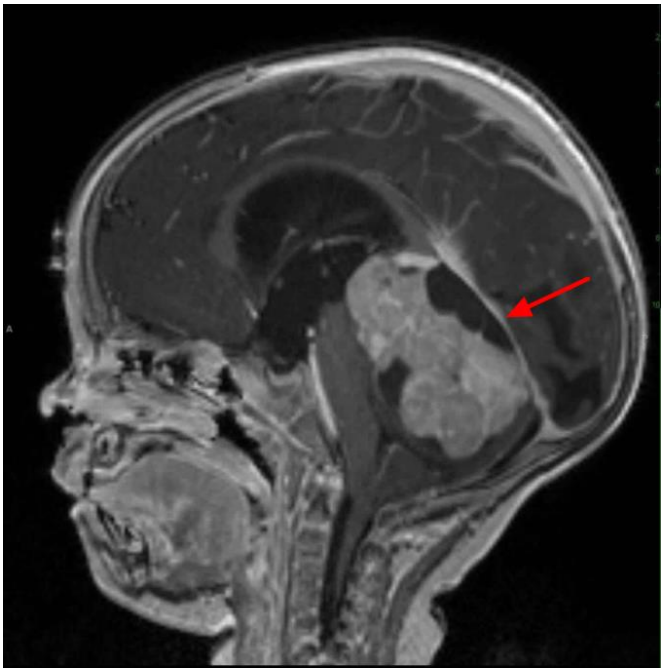
Fact Sheet
on
Medulloblastoma

Introduction

Medulloblastomas are the most common malignant brain tumour of childhood and occur exclusively in the cerebellum. The disease is rare after the fourth decade of life.



Patients with medulloblastoma present with a combination of signs and symptoms of increased intracranial pressure and cerebellar dysfunction evolving over a period of weeks to a few months.

[Picture Credit: Medulloblastoma]

Medulloblastomas by definition occur in the cerebellum, which is the part of brain located at the base of the skull, just above the brainstem. The cerebellum is involved in many functions including coordination of voluntary movements (e.g., walking, fine motor skills) and regulating balance and posture. Medulloblastomas arise from primitive, undeveloped cells in the brain. Most medulloblastomas occur in infants and children. Less commonly, these tumours can develop in adults as well.

Medulloblastoma

Medulloblastoma is a cancerous tumour. It is also called Cerebellar Primitive Neuroectodermal Tumour (PNET) that starts in the region of the brain at the base of the skull, called the posterior fossa. These tumours tend to spread to other parts of the brain and to the spinal cord. Medulloblastoma accounts for 64.3% of all embryonal tumours in paediatric patients (0-19 years old).

Males display a higher incidence rate relative to females (males: 0.16 vs. females: 0.12), except in patients <1 year-old. Overall ratio tend to be 1.5:1 for males. Males also tend to have poorer prognosis.

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Penas-Prado, M., Armstrong, T.S. & Gilbert, M.R. 20-20.
"Medulloblastoma is a rare brain tumor that occurs in both children and adults, with patients aged 15 to 39 years accounting for 30% of all cases. In adults, guidelines for diagnosis and treatment are often based on retrospective data and extrapolated from the pediatric experience due to limited availability of prospective trials or registries involving adults. Importantly, adult patients differ from pediatric patients in many aspects, including the molecular features of the tumor and tolerance to treatment. In 2017, the NCI was granted support from the Cancer Moonshot initiative to address the challenges and unmet needs of adults with rare central nervous system (CNS) tumors through the NCI Comprehensive Oncology Network for Evaluating Rare CNS Tumors (NCI-CONNECT). On November 25, 2019, NCI-CONNECT convened a multidisciplinary workshop on adult medulloblastoma. Working groups identified unmet needs in clinical care and research and developed specific action items, including a proposal for inclusion of new items in the NCCN Guidelines for Adult Medulloblastoma, delineated in this review along with the evidence supporting their incorporation. Recommendations included facilitating referral of patients to centers of excellence; promoting patient participation in clinical trials or registries; encouraging use of DNA methylation for confirmation of diagnosis and subgrouping; offering counseling on contraception and fertility preservation; evaluating patients for symptoms and medical management of endocrine, vision, hearing, and neurocognitive deficits; providing psychosocial support and referral to neurorehabilitation; minimizing delays in therapy; and incorporating imaging standards and criteria for progression."

Northcott, P.A., Robinson, G.W., Kratz, C.P., Mabbott, D.J., Pomeroy, S.L., Clifford, S.C., Rutkowski, S., Ellison, D.W., Malkin, D., Taylor, M.D., Gajjar, A. & Pfister, S.M. 2019.
"Medulloblastoma (MB) comprises a biologically heterogeneous group of embryonal tumours of the cerebellum. Four subgroups of MB have been described (WNT, sonic hedgehog (SHH), Group 3 and Group 4), each of which is associated with different genetic alterations, age at onset and prognosis. These subgroups have broadly been incorporated into the WHO classification of central nervous system tumours but still need to be accounted for to appropriately tailor disease risk to therapy intensity and to target therapy to disease biology. In this Primer, the epidemiology (including MB predisposition), molecular pathogenesis and integrative diagnosis taking histomorphology, molecular genetics and imaging into account are reviewed. In addition, management strategies, which encompass surgical resection of the tumour, cranio-spinal irradiation and chemotherapy, are discussed, together with the possibility of focusing more on disease biology and robust molecularly driven patient stratification in future clinical trials."

Incidence of Medulloblastoma in South Africa
The South African National Cancer Registry (2017) does not provide any information regarding the incidence of Medulloblastoma.

- The majority of medulloblastomas occur as sporadic cases, yet hereditary conditions have been associated with medulloblastoma, including:
  Gorlin syndrome (nevoid basal-cell carcinoma syndrome)
- Blue rubber-bleb nevus syndrome
- Turcot syndrome (i.e., glioma polyposis syndrome)
- Rubinstein-Taybi syndrome

Mahapatra, S. & Amsbaugh, M.J. 2020.
"While leukemias are the most common type of malignancy to afflict the pediatric population, brain tumors are the most common solid tumors in this age group. Medulloblastoma is the most common malignant brain tumor in children constituting nearly 20% of all pediatric brain tumors. It is categorized as an embryonal

neuroepithelial tumor of the cerebellum. This is a high-grade tumor that has a propensity to spread via the cerebrospinal fluid. Within the first few years of diagnosis, mortality approximates 15%; however, cure rates can reach as high as 60% with current therapeutic modalities. Surgical resection preceded and/or followed by radiation and chemotherapy is the mainstay of therapy, with five-year survival rates of between 50% to 90%. This wide range is multifactorial, owing in part to age at diagnosis, the presence of metastases at diagnosis, and a histologic variant of medulloblastoma. Regardless of long-term survival, treatment-related cognitive, neurologic, and endocrinologic effects remain a debilitating concern and an impetus for the search for further therapeutic modalities."

Risk Factors for Medulloblastoma

Doctors are gradually understanding what causes most childhood tumours, including medulloblastoma. The following factors are linked with a higher risk of medulloblastoma:

- Gender. Medulloblastoma is more common in boys than in girls.
- Age. Medulloblastoma occurs most often in the first 8 years of life, with about half occurring in children younger than 6 years old.
- Genetics**.** The following genetic conditions are associated with a higher risk of developing medulloblastoma:
    - Nevoid basal cell carcinoma syndrome (NBCCS)
    - Turcot syndrome (a subtype of familial adenomatous polyposis) – (FAP)
    - BRCA1 gene mutations.
    - genetic conditions, such as Gorlin and Li-Fraumeni syndromes
    - Nearly half of childhood medulloblastomas have a genetic abnormality on chromosome 17

Signs and Symptoms of Medulloblastoma

Symptoms are often progressive over weeks to months, and it is not uncommon for patients to have an extended symptomatic period prior to initial diagnosis. Metastatic disease is commonly present at diagnosis (40%), and imaging of the entire craniospinal axis is an essential part of the initial diagnostic evaluation.

Symptoms usually differ by anatomic location of the tumour, presence of disseminated disease, and by the presence of hydrocephalus (condition in which excess cerebrospinal fluid (CSF) builds up within the brain).

If a child has Medulloblastoma, the following symptoms may occur:

- Headaches
- Morning nausea or vomiting that gradually gets worse
- Clumsiness
- Problems with handwriting
- Visual problems (rare) at the time of diagnosis
- Morning headache or headache that goes away after vomiting.
- Unusual sleepiness or change in energy level.
- Change in personality or behaviour.

If the tumour has spread to the spinal cord, additional symptoms may include:

- Back pain

- Trouble walking
- Problems controlling bladder and bowel functions

Physical signs may include:

- Physiognomy (facial features or expression)
    - Increasing head circumference often is the only presenting symptom in infants.
    - Infants may have also full anterior fontanelles with split cranial sutures.
- Funduscopic examination
    - Visual difficulty usually is due to papilloedema (optic disc swelling); however, it also may originate from cranial nerve palsy (most commonly Cranial Nerve IV or VI).
    - Some studies have found papilloedema (the most common physical finding) to be present in as many as 90% of patients.
- Extraocular examination
    - As a consequence of hydrocephalus, the sixth cranial nerve can be compressed at the petroclival ligament, resulting in diplopia (double vision) and lateral gaze paresis.
    - Fourth cranial nerve palsy can be detected on careful extraocular examination and should be considered in any patient with a head tilt.
    - Patients with fourth cranial nerve dysfunction have greatest difficulty when eyes are rotated medially and depressed (i.e., going down stairs). The fourth cranial nerve usually is compressed by direct tumour extension into the cerebral aqueduct.
    - Examination of the extraocular muscles may detect nystagmus (involuntary eye movement), which, although nonspecific, can be related to a lesion of the cerebellar vermis.
- Cerebellar signs
    - Medulloblastoma most commonly is located midline. Therefore, unilateral dysmetria (lack of coordination of movement typified by the undershoot or overshoot of intended position with the hand, arm, leg, or eye) is less common than either truncal ataxia (impaired balance or coordination) or a wide-based gait (way of walking). Latter symptoms are easily observable on tandem gait (method of walking or running where the toes of the back foot touch the heel of the front foot at each step).
    - Desmoplastic medulloblastoma is more common in adults and usually arises in the cerebellar hemisphere.
    - Signs of ipsilateral (belonging to, or occurring on the same side of the body) cerebellar dysfunction in the arm or the leg are more common in this subtype.
- Torticollis: Head tilt can be a manifestation of either accessory nerve (cranial nerve eleven) or trochlear nerve (cranial nerve four) palsy (paralysis).

Diagnosis of Medulloblastoma

Magnetic resonance imaging (MRI) typically demonstrates a midline or paramedian cerebellar mass that enhances after contrast administration, and approximately one third of patients will have evidence of tumour dissemination through the subarachnoid space either by imaging or cerebrospinal fluid (CSF) examination.

Treatment of Medulloblastoma

Treatment of childhood medulloblastoma in children younger than 3 years of age is usually within a clinical trial and may include the following:

- Surgery followed by chemotherapy to delay radiation therapy.
- Surgery followed by high-dose chemotherapy with stem cell transplant.
- Chemotherapy only.

Kabir, T.F., Kunos, C.A., Villano, J. & Chauhan, A. 2020.

Background: Immune-mediated therapies have transformed the treatment of metastatic melanoma and renal, bladder, and both small and non-small cell lung carcinomas. However, immunotherapy is yet to demonstrate dramatic results in brain tumors like medulloblastoma for a variety of reasons. Recent pre-clinical and early phase human trials provide encouraging results that may overcome the challenges of central nervous system (CNS) tumors, which include the intrinsic immunosuppressive properties of these cancers, a lack of antigen targets, antigenic variability, and the immune-restrictive site of the CNS. These studies highlight the growing potential of immunotherapy to treat patients with medulloblastoma, a disease that is a frequent cause of morbidity and mortality to children and young adults.

Methods: We conducted an inclusive review of the PubMed-indexed literature and studies listed in clinicaltrials.gov using combinations of the keywords medulloblastoma, immunotherapy, CNS tumors, brain tumors, vaccines, oncolytic virus, natural killer, and CAR T to identify trials evaluating immunotherapy in preclinical experiments or in patients with medulloblastoma. Given a limited number of investigations using immunotherapy to treat patients with medulloblastoma, 24 studies were selected for final analysis and manuscript citation.

Results: This review presents results from pre-clinical studies in medulloblastoma cell lines, animal models, and the limited trials involving human patients.

Conclusion: From our review, we suggest that cancer vaccines, oncolytic viral therapy, natural killer cells, and CAR T therapy hold promise against the innate immunosuppressive properties of medulloblastoma in order to prolong survival. There is an unmet need for immunotherapy regimens that target overexpressed antigens in medulloblastoma tumors. We advocate for more combination treatment clinical trials using conventional surgical and radiochemotherapy approaches in the near-term clinical development.

Liu, X., Ding, C., Tan, W. & Zhang, A. 2020.

"Medulloblastoma (MB) is the most common childhood malignant brain tumor, accounting for approximately 20% of all pediatric central nervous system tumors. Current standard treatments involving surgical interventions followed by craniospinal irradiation and adjuvant chemotherapy have severe motor and cognitive defects. Therefore, individualized treatment regimens with reduced toxicity designed according to the presence of specific oncogenic 'driver' genes are urgently demanded. To this end, recent genetic and epigenetic findings have advanced the classification of MB into the international consensus of four distinct MB molecular subgroups (WNT, SHH, Group 3, and Group 4) based on their respective molecular and histopathological characteristics. More recent studies have indicated that up to seven molecular subgroups exist in childhood MB. Moreover, studies on the inter- and intra-tumoral features of the four subgroups revealed that each subgroup contains variant subtypes. These results have greatly helped risk stratification of MB patients at diagnosis and significantly improved clinical treatment options. Herein, we highlight the recent advances and challenges associated with MB classification, and the development of therapeutic treatments targeting novel subgroup-specific molecular and epigenetic factors, especially those in the SHH-driven MB tumors."

Nobre, L., Pauck, D., Golbourn, B., Maue, M., Bouffet, E., Remke, M. & Ramaswamy V. 2019.
"Most medulloblastoma protocols worldwide include vincristine during radiation and chemotherapy. A significant dose-limiting toxicity is peripheral neuropathy; however, there is a paucity of data to support the view that omission of vincristine does not impact survival. Herein we report two adolescent patients with Group 4 and SHH medulloblastoma, where vinblastine successfully replaced vincristine with resolution of their peripheral neuropathy. We furthermore show vinblastine is highly active in vitro and demonstrates equivalent antitumoral activity compared to vincristine. Substitution of vincristine with vinblastine in future studies should be considered for all patients with medulloblastoma, particularly those with hereditary neuropathy, severe vincristine toxicity, and adults."

Eckerdt, F., Bell, J.B., Beauchamp, E.M., Clymer, J., Blyth, G.T., Kosciuczuk, E.M., Ma, Q., Chen, D.Z., Horbinski, C., Goldman, S., Munshi, H.G., Hashizume, R. & Platanias, L.C. 2019.
"Medulloblastoma is a highly malignant pediatric brain tumor associated with poor outcome. Developing treatments that target the cancer stem cell (CSC) population in medulloblastoma are important to prevent tumor relapse and induce long-lasting clinical responses. We utilized medulloblastoma neurospheres that display CSC characteristics and found activation of the PI3K/AKT pathway in sphere-forming cells. Of all class I_A PI3Ks, only the PI3Kα isoform was required for sphere formation by medulloblastoma cells. Knockdown of p110α, but not p110β or p110δ, significantly disrupted cancer stem cell frequencies as determined by extreme limiting dilution analysis (ELDA), indicating an essential role for the PI3Kα catalytic isoform in medulloblastoma CSCs. Importantly, pharmacologic inhibition of the MAPK-interacting kinase (MNK) enhanced the antineoplastic effects of targeted PI3Kα inhibition in medulloblastoma. This indicates that MNK signaling promotes survival in medulloblastoma, suggesting dual PI3Kα and MNK inhibition may provide a novel approach to target and eliminate medulloblastoma CSCs. We also observed a significant reduction in tumor formation in subcutaneous and intracranial mouse xenograft models, which further suggests that this combinatorial approach may represent an efficient therapeutic strategy for medulloblastoma.**Implications:** These findings raise the possibility of a unique therapeutic approach for medulloblastoma, involving MNK targeting to sensitize medulloblastoma CSCs to PI3Kα inhibition."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

Thompson, E.M., Ashley, D. & Landi, D. 2020.
"Medulloblastoma is a heterogeneous disease with at least four distinct molecular subgroups: wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. Recently there has been considerable progress defining the

molecular drivers and prognostic factors of each subgroup. However, this information has only rarely been used to stratify risk or impact treatment. The purpose of this work is to provide an update on current clinical trials that provide molecularly stratified treatment paradigms. A search was conducted on ClinicalTrials.gov using the following search terms: "medulloblastoma and subgroup", "medulloblastoma and SHH", "medulloblastoma and WNT", and "medulloblastoma and Non-WNT/Non-SHH". This search resulted in nine distinct clinical trials, five for newly diagnosed medulloblastoma and four for recurrent medulloblastoma. Four trials for newly diagnosed medulloblastoma had a component of craniospinal irradiation reduction for patients with WNT medulloblastoma. Molecularly stratified trials for recurrent medulloblastoma largely focus on SHH. As these trials are ongoing, there are limited data available. A trial in which newly-diagnosed WNT patients received modest chemotherapy without radiation has been closed to accrual due to several early failures. Phase II trials evaluating vismodegib for SHH medulloblastoma in children and adults have been disappointing. In conclusion, although there is an expanding array of clinical trials which incorporate molecular data in prescribing treatment for newly-diagnosed and recurrent medulloblastoma, treatments for these diseases are fairly uniform, with craniospinal radiation dose being the main variable. As the drivers of the distinct subgroups and their associated prognoses are better elucidated, future clinical trials and novel targeted agents are needed to improve outcomes and reduce toxicity where feasible."

Medical Disclaimer

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Sources and References Consulted and/or Utilised

Eckerdt, F., Bell, J.B., Beauchamp, E.M., Clymer, J., Blyth, G.T., Kosciuczuk, E.M., Ma, Q., Chen, D.Z., Horbinski, C., Goldman, S., Munshi, H.G., Hashizume, R. & Platanias, L.C. 2019. Potent antineoplastic effects of combined P13Kα-MNK inhibition in medulloblastoma. *Mol Cancer Res*. 2019 Mar 6. doi: 10.1158/1541-7786.MCR-18-1193. [Epub ahead of print]

Kabir, T.F., Kunos, C.A., Villano, J. & Chauhan, A. 2020. Immunotherapy for medulloblastoma: current perspectives. *Immunotargets Ther.* 2020 Apr 20;9:57-77.

Liu, X., Ding, C., Tan, W. & Zhang, A. 2020. Medulloblastoma: Molecular understanding, treatment evolution, and new developments. *Pharmacol Ther*. 2020 Jun;210:107516.

Mahapatra, S. & Amsbaugh, M.J. 2020. Medulloblastoma. ***In***: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan. 2020 Jul 3.

Medullablastoma
https://www.stjude.org/disease/medulloblastoma.html
https://emedicine.medscape.com/article/1181219-overview#a6
https://emedicine.medscape.com/article/1181219-overview
https://www.cancer.net/cancer-types/medulloblastoma-childhood/risk-factors
https://www.columbianeurosurgery.org/conditions/childhood-medulloblastoma/causes/
https://www.mdanderson.org/cancer-types/medulloblastoma.html
https://www.uptodate.com/contents/clinical-presentation-diagnosis-and-risk-stratification-of-medulloblastoma
https://rarediseases.org/rare-diseases/medulloblastoma/
https://www.cancer.org/cancer/brain-spinal-cord-tumors-children/causes-risks-prevention/risk-factors.html
https://www.dovemed.com/diseases-conditions/medulloblastoma-childhood/
https://www.who.int/peh-emf/meetings/archive/en/mckinney.pdf
https://thejns.org/pediatrics/view/journals/j-neurosurg-pediatr/20/1/article-p35.xml
http://www.bioline.org.br/pdf?ni06003
https://academic.oup.com/nop/article/4/2/82/2631784
https://blog.cirm.ca.gov/2019/01/25/targeted-treatment-for-pediatric-brain-tumors-shows-promising-results/
https://www.stanfordchildrens.org/en/topic/default?id=childhood-medulloblastoma-treatment-pdq-37-CDR0000062776

Nobre, L., Pauck, D., Golbourn, B., Maue, M., Bouffet, E., Remke, M. & Ramaswamy V. 2019. Effective and safe tumor inhibition using vinblastine in medulloblastoma. *Pedatr Blood Cancer*. 2019 Jun;66(6):e27694. doi: 10.1002/pbc.27694. Epub 2019 Mar 8.

Northcott, P.A., Robinson, G.W., Kratz, C.P., Mabbott, D.J., Pomeroy, S.L., Clifford, S.C., Rutkowski, S., Ellison, D.W., Malkin, D., Taylor, M.D., Gajjar, A. & Pfister, S.M. 2019. Medulloblastoma. *Nat Rev Dis Primers*. 2019 Feb 14;5(1):11. doi: 10.1038/s41572-019-0063-6. Review.

Penas-Prado, M., Armstrong, T.S. & Gilbert, M.R. 20-20. Proposed additions to the NCCN Guidelines for adult medulloblastoma. *J Natl Compr Canc Netw*. 2020 Nov 2;18(11):1579-1584.

Quinlan, A. & Rizzolo, D. 2017. Understanding medulloblastoma. *JAAPA*. 2017 Oct;30(10):30-36. doi: 10.1097/01.JAA.0000524717.71084.50.

Sherif, R.S., Elshemey, W.M. & Attalla, E.M. 2018. The risk of secondary cancer in pediatric medulloblastoma atients due o three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. *Indian J Cancer*. 2018 Oct-Dec;55(4):372-376. doi: 10.4103/ijc.IJC_410_18.

Thompson, E.M., Ashley, D. & Landi, D. 2020. Current medulloblastoma subgroup specific clinical trials. *Transl Pediatr.* 2020 Apr;9(2):157-162.