Medulloblastoma

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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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Medulloblastoma: Diagnosis, Treatment And Prognosis

Graduate Thesis

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This graduate thesis was made at the Department of Neurosurgery KBC Rebro, University Hospital Centre Zagreb, mentored by doc. dr. sc. Goran Mrak, and was submitted for evaluation during the academic year 2015/2016.

ABBREVIATIONS

MRI	magnetic resonance imaging
CT	computed tomography
PNET	primary neuroectodermal tumor
WHO	world health organization
CSF	cerebral spinal fluid
EVD	external ventricular drain
H&E	hematoxylin and eosin stain
GY	gray unit

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SUMMARY

Title: Medulloblastoma: Diagnosis, Treatment and Prognosis
Key words: Medulloblastoma, Neurooncology, Posterior fossa tumor, Surgical treatment.
Author: Benjamin Aksungur

Medulloblastomas are embryonal tumors arising from the cerebellum and are the most common malignant brain tumors of childhood, with an incidence of 10-25% of primary CNS neoplasms. Medulloblastomas in adults are less common but they do occur. Like many tumors the exact cause is unknown but changes have been identified in genes and chromosomes that may play a role in the development of these tumors. Although the cause is unknown there are several studies that have ruled out many environmental factors. Medulloblastomas are diagnosed by clinical presentation as well as diagnostic tools. Patients with medulloblastoma present with a history of headaches, emesis, and lethargy which are commonly subtle and intermittent. Symptoms are most often related to hydrocephalus secondary to obstruction of the fourth ventricle. Diagnostic tools such as the CT and MRI play a significant role in helping to initially diagnose medulloblastoma as well as the workup following the treatment and or resection. Histologically medulloblastomas can be classified into 7 different types, which is important for further treatment. The definitive diagnosis of medulloblastoma is made on microscopic pathologic examination. Current treatment of medulloblastoma consists of surgically removing as much of the tumor as possible, followed by craniospinal radiation and or chemotherapy. Treatment plans are based on factors that indicate the risk of recurrence. How well a patient responds to treatment is affected in general by their age at the time of diagnosis, the size and extent of the tumor, the amount of mass that can be removed safely and the level of metastatic disease. It is now becoming clear that patients with certain subgroups of medulloblastomas have better long-term outcome in comparison to the others.

1. INTRODUCTION

While medulloblastoma is rare, it is the most common pediatric malignant brain tumor. It is a highly invasive neuroendothelial tumor that arises in the cerebellum located in the posterior fossa. This area is responsible for controlling balance posture and complex motor functions. Tumors located in this area of the brain are referred to as infratentorial tumors. This means that the tumor is located below the tentorium, which is a thick membrane that separates the larger cerebral hemisphere of the brain from the cerebellum. Medulloblastomas arise predominantly from the cerebellar vermis, which is a narrow worm like bridge that connects the cerebellum's two sides. Wheras in adults it mostly arises in the body of the cerebellum, especially towards the edges.[1] Medulloblastomas where previously classified as a PNETs however recent data has shown that these tumors are biologically distinct from other PNETs.[2] It was introduced in 1925 by Bailey and Cushing and initially considered a subtype of gliomas and called spongioblastoma cerabelli and was later renamed to medulloblastoma.[3] Over the years there has been significant debate about the most appropriate classification for small round cell tumors of the posterior fossa. It was found that histologically similar or identical tumors could be found in other areas of the brain, and collectively would be classfied as PNETs and subdivided on the basis of location, histologcal or clinical features.[4] More recently studies have shown that tumors which arise in the posterior fossa are molecularly different than those arising in other regions of the brain. Medulloblastomas are now considered an entity that only arises in the posterior fossa. The WHO defines medulloblastoma as a malignant invasive embryonal tumor of the cerebellum with prefrential manifestion in children, predominantly neuronal differentiation and inherent tendancy to metastisaze via CSF with several subtypes.[5] Due to the fact that they are classified into subgroups the treatment has moved away from a ”one therapy fits all” towards a more subgroup driven therapy.

2. AETIOLOGY

In general the aetiology of medulloblastoma remains unknown. These tumors form because of errors in the machinery in the cell that controls the growth and death. Changes have been identified in genes and chromosomes that may play a role in development, for example one half of all pediatric medulloblastomas contain alterations to portions of chromosome 17 while a much smaller proportion of tumors about 10% have a solitary deletion of chromosome 6.[6] Inherited and familial medulloblastoma is extremely rare, nevertheless there are a few rare inherited health syndromes that are associated with increased risk for developing this tumor. Some examples of syndromes that contain specific genetic changes are Gorlins syndrome (PTCH1), Li Freumeni syndrome (p53), Turcots syndrome A (APC) and Rubenstein Taybi syndrome (CBP).[7] While these syndromes are inherited the majority of medulloblastomas are not. However through the study of these syndromes genetic changes have been identified in medulloblastomas. With this advent of integrated genetics, studies have revealed that this tumor comprises at least four variants, which are transcriptionally, genetically, and clinically distinct. The four subgroups are termed, WNT, sonic hedgehog (SHH), group 3, group 4.[2] The fact that the different molecular subgroups have been found to have a varied outcome is the most important recent discovery of medulloblastoma. These subgroups have significant prognostic values and predict survival independently of the presence of metastasis or unfavorable histology. Despite the fact that research has been conducted and the exact causes are unknown, several studies have ruled out environmental factors, including: aspartame, artificial sweeteners, smoking, alcohol or diet during pregnancy.[6]

Medulloblastomas comprise approximately 25% of all pediatric brain tumors. No racial predispositions has been noted.[8] Medulloblastoma can occur in all age groups with a peak age of incidence 3-5 years, most common in children younger than 9 years of age with a decreasing incidence after this age. Approximately 80% are diagnosed within the first 15 years of age. Medulloblastomas are not common in adults, but it does occur. One-fourth of diagnosed cases are found in adults between the ages of 20-44. The incidence in adults significantly declines after the age of 45. There exists a modest male preponderance in a ratio of 1.4:1, which is most noticeable in children younger than age 4.[6]

3. DIAGNOSIS

3.1. Clinical Presentation

The clinical signs and symptoms initially seen with medulloblastoma are mostly asymptomatic or cause subtle clinical symptoms. Once symptoms do arise they are usually related to hydrocephalus secondary to obstruction of the fourth ventricle. Arising most commonly from the area of the cerebellar vermis, medulloblastomas cause neurologic symptoms by filling the fourth ventricle and blocking CSF egress or infiltrating cerebellar tissue.[3] Most tumors are diagnosed when they are quite large and obstruct the flow of CSF. Symptoms are usually vague such as headaches, nausea or vomiting, problems with motor skills, tiredness, tilting of the head to one side, walking difficulty and balance problems. Almost all children with medulloblastoma present with symptoms of increased intracranial pressure specifically early morning vomiting and headache. The common sequence of events is early morning headache relieved by vomiting and resolution of symptoms. As the tumor progresses, the diurnal variation of the headache and vomiting tends to become less pronounced, and these symptoms are more constant.[2] Other symptoms depend on the nerves and brain structures affected by the tumor. Since medulloblastomas appear in the cerebellum, the center of balance and movement, problems with dizziness and coordination are common. In addition to vomiting and headache truncal ataxia and diplopia secondary to sixth nerve palsy are also common presenting features. More lateral lesions may present with appendicular ataxia and occasionally focal weakness. Other neurologic symptoms localizing to the posterior fossa and brainstem can be present at diagnosis; nevertheless, they are much less common. Seizures rarely occur in children with medulloblastoma, and it is much more common for decerebrate posturing to be misinterpreted as tonic seizure. The time to diagnosis varies; nonetheless, children typically present acutely, and most often do not have a prediagnostic interval of longer than 2 months. Longer diagnostic times to not correlate to a poorer prognosis and consequences.

The differential diagnosis for medulloblastoma at presentation includes ependymoma, pilocytic astrocytoma, atypical teratoid/rhabdoid tumor (AT/RT), and embryonal tumor with abundant neuropil and true rosettes (ETANTR).[2] It can be difficult to differentiate these tumors based on clinical symptoms alone, even though children with pilocytic astrocytomas tend to have a longer duration of symptoms alone, and children with ependymomas have a history of neck pain or stiffness with associated torticollis due to caudal invasion of the tumor through the foramen magnum.

Infants and very young children present with a somewhat different clinical presentation. Due to their open sutures, infants present with macrocephaly and a head circumference that crosses percentiles. Infants with open sutures may present with irritability lethargy, bulging fontanels, downward gaze due to pressure on the pretectum, and developmental arrest or regression.[1] Very young children also tend to present with more symptoms of hydrocephalus, such as apnea, bradycardia, and loss of consciousness, because of a more advanced stage of disease at diagnosis secondary to an increased tolerance of hydrocephalus. Adults commonly present with atypical symptoms and a longer prediagnostic interval because of a higher incidence of desmoplastic disease, which can arise in more lateral regions of the cerebellum.

Metastasis may present with symptoms of nerve root involvement or spinal cord symptoms, and is present in about 40% of patients at the time of diagnosis, most commonly being asymptomatic. Recurring disease is rarely diagnosed clinically; instead, it is diagnosed on routine serial neuroimaging, and the likelihood of recurrence decreases with time.[9]

The vast majority of medulloblastoma cases are sporadic (non-inherited). However, a small proportion of medulloblastoma cases occur in the context of hereditary syndromes which have an increased risk of cancer. Syndromes known to be associated with medulloblastoma include the following[10]:

Disease	Gene(s)	Notes
Basal Cell Nevus Syndrome	PTCH1 SMO SUFU PTCH2	Basal Cell Nevus Syndrome (also known as Gorlin Syndrome) is an autosomal dominant condition characterised by the appearance of basal cell carcinomas, together with skeletal abnormalities, odontogenic keratocysts and increased risk of Medulloblastoma. Medulloblastoma develops in about 5 out of every 100 children with the syndrome.
Fanconi Anaemia	BRCA2 FANCD2 PALB2 FANCC FANCA	Fanconi Anemia (FA) is a rare autosomal recessive genetic disorder characterised clinically by progressive bone marrow failure, skeletal deformities and a predisposition to leukaemia and a wide range of cancers. Affected children usually develop severe aplastic anemia by age 8 to 9 years.
Li-Fraumeni syndrome	TP53	A rare inherited autosomal dominant disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults. The most frequent types of cancer associated with Li-Fraumeni syndrome are breast cancer, osteosarcoma, and soft tissue sarcomas. People affected also have increase risk of brain tumuors, leukaemias, adrenocortical carcinoma and other types of cancer.
Rubinstein-Taybi Syndrome	CREBBP EP300	Rubinstein-Taybi Syndrome (RTS) ia an autosomal dominant chromosomal disorder characterized by broad thumbs, webbing of fingers and toes, mental retardation, beaked nose, short upper lip, pouting lower lip. Individuals with RTS have an increased risk of brain tumors and occasionally other tumours. Approximately 5 % of RTS patients develop a malignancy or a benign tumor.
Turcot Syndrome	MLH1 PMS2 APC MSH2 MSH6	Turcot Syndrome is characterised by malignant tumors of the central nervous system (mostly astrocytomas and medulloblastoma) associated with familial polyposis of the colon. There are different sub-types.

3.2. Imaging

Initially the diagnosis of medulloblastoma is usually made with non-contrast CT followed by MRI. On a noncontrast CT scan, a medulloblastoma is typically a hyperattenuating midline mass surrounded by vasogenic edema; it enhances homogeneously following the administration of contrast. Lateral cerebellar medulloblastomas are usually of desmoplastic histology. In at least 95% of patients hydrocephalus is present on the initial CT scan. CT findings for medulloblastoma are not specific and are difficult to distinguish from ependymoma or AT/RT.[11]

For posterior fossa tumors the preferred method of initial evaluation is an MRI with gadolinium enhancement (Fig.1,2,3). On T1-weighted MR imaging, medulloblastomas are hypointense or isointense relative to gray matter and become hyperintense with the administration of gadolinium. On T2-weighted imaging, the signal is variable and can be hyperintense to hypointense relative to gray matter.[2]

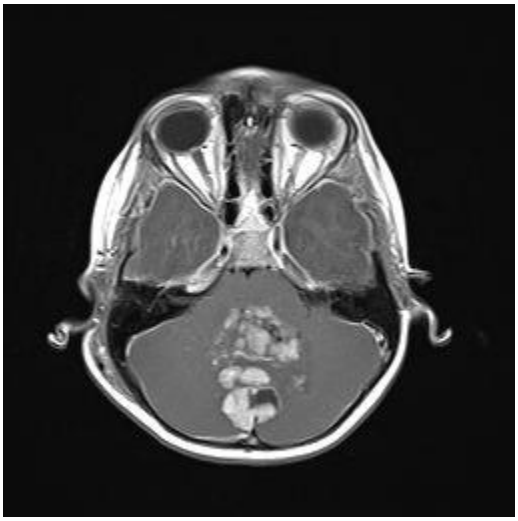


Fig.1 – Axial MRI with gadolinium in patient with medulloblastoma

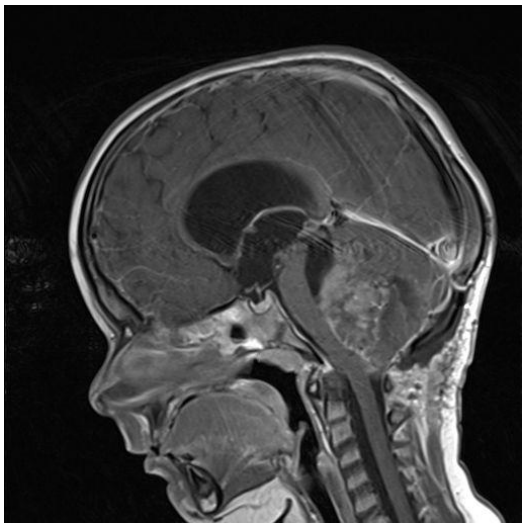


Fig. 2 –Sagittal MRI with gadolinium in patient with medulloblastoma

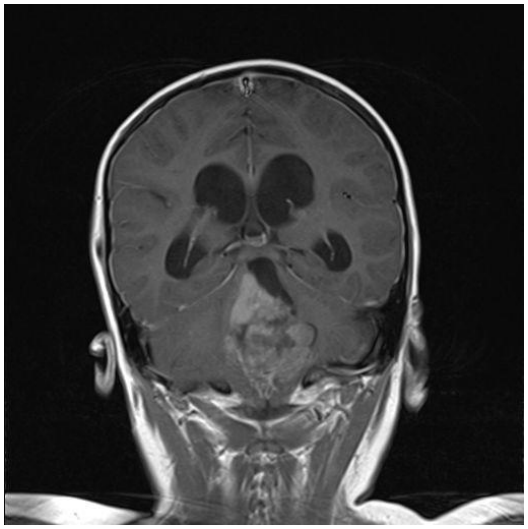


Fig. 3 – Coronal MRI with gadolinium in patient with medulloblastoma

In differentiating medullolastoma from ependymoma or astrocytoma, diffusion weighted imaging can be very useful. Because medulloblastomas consist of dense small round cells with minimal cytoplasm and reduced free water, they exhibit diffusion restriction with a reduced apparent diffusion coefficient. Whereas ependymomas and pilocytic astrocytomas characteristically do not have restricted diffusion.[2] AT/RTs also display restricted diffusion; conversely, young age of the patient, cerebellopontine angle involvement, and intratumoral hemorrhage can help distinguish AT/RTs from medulloblastomas radiologically.[11] Due to the fact that 40% of meduloblastomas are metastatic at

the time of diagnosis, perioperative imagining of the entire craniospinal axis is desirable so that adequate staging can be established, when feasible. To avoid the possibility of false-positives due to debris and blood products, the imaging of the entire craniospinal axis should be performed 2 weeks or later postoperatively for full staging.[12] Cranial MR imaging should also be repeated within 72 hours postoperatively or after 2 weeks postoperatively because a residual tumor of more than 1.5 cm^2 may be correlated with a higher risk for disease, if performed between 3-14 days there is a risk of false positive.[12] For a conclusive diagnosis, pathologic diagnosis is required.

Lumbar CSF is also acceptable in every patient diagnosed with medulloblastoma. Lumbar sampling is preferred over ventricular sampling at surgery or through a shunt because lumbar CSF sampling is more sensitive than ventricular sampling.[13] Preferably, both ventricular CSF sampling at surgery and lumbar CSF sampling 2 weeks postoperatively should be obtained because the two sites can contraindicate each other, and a positive ventricular CSF cytology intraoperatively has been associated with a poorer outcome.[13]

If extraneural disease is suspected, FDG-PET (fluorodeoxyglucose F 18 positron emission tomography) and bone marrow biopsy are the preferred modalities. Extraneural disease is present more commonly at recurrence, predominantly very late recurrences, and can be present in the absence of intracranial disease.[14] Due to ototoxic and nephrotoxic effects of both platinum-based chemotherapy and radiotherapy, hearing and creatinine clearance should be evaluated postoperatively in all patients before the initiation of either chemotherapy or radiotherapy.

3.3.Hydrochepalus

Patients with medulloblastoma most commonly have symptoms related to increased intracranial pressure (as a consequence of hydrocephalus) (Fig.4). Symptoms usually precede presentation by no more than 2 months. As such, the management of hydrocephalus is usually the first step. Symptoms that present in relation to hydrocephalus, are related to the age of the patient.

Younger non-verbal patients present with behavioral changes. Symptoms in younger children include lethargy, irritability, vomiting, and decreased social interactions. Older children and adults complain of headache, especially upon awakening in the morning. Vomiting without nausea is more common in the morning, since being recumbent increases intracranial pressure. Patients may develop double vision as the sixth cranial nerve becomes stretched from the hydrocephalus. Visual disturbances more commonly are a result of papilledema.

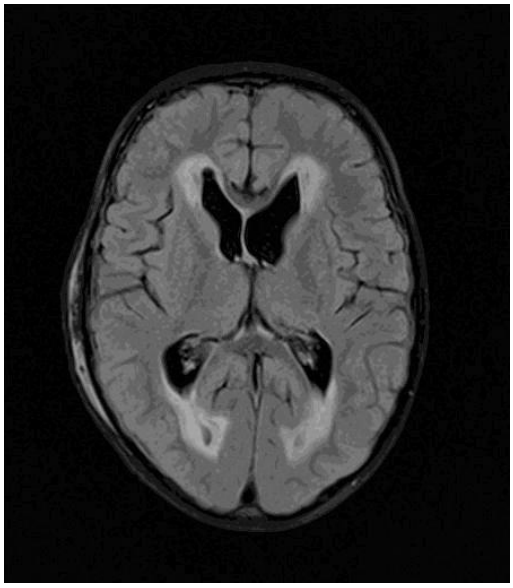


Fig.4 - Periventricular hypointensity suggesting hydrocephalus

Most patients can be managed with preoperative dexamethasone (0.45 mg/kg per day divided into three doses, with an initial dose of 0.45 mg/kg), which results in significant alleviation of the symptoms and a reduction in vomiting. Placing an EVD preoperatively is occasionally necessary. When an EVD is placed, consideration must be given to the possibility of upward herniation, and the rate and quantity of CSF drainage must be carefully monitored. During the postoperative period the height of an EVD can be gradually increased, and in most cases the EVD can be successfully removed within a week to 10 days postoperatively.[15] Routine ventriculoperitoneal shunting is not indicated perioperatively, as 10 to 40% of children require permanent CSF diversion postoperatively. Among the indications for shunting are, young children and in those with very large ventricles at diagnosis, more extensive tumors, and metastatic disease[15]. When persistent hydrocephalus is

present, either ventriculoperitoneal shunting or endoscopic third ventriculostomy can be considered.[16] Several series have reported high success rates with endoscopic third ventriculostomy for persistent hydrocephalus, and it should be considered in patients requiring postoperative shunting who are suitable candidates for this procedure.

4. CLASSIFICATION, STAGING AND PATHOLOGY

Pathology

Microscopic pathologic examination remains the primary way of making a definitive medulloblastoma diagnosis. The characteristic microscopic appearance is that of a “small round blue cell tumor” which is morphologically indistinguishable from supratentorial PNETs or pineoblastomas. Histologically, there are three main types of medulloblastoma: (1) classic (Fig.5), (2) desmoplastic (Fig.6), and (3) large cell/anaplastic (Fig.7). The classic variant is by far the most common histology (>70%), while desmoplastic histology is more common in infants and adults and is most commonly associated with the SHH pathway activation. Large cell/anaplastic medulloblastoma is aggressive and more common in the group 3 molecular subgroup with a poor prognosis.

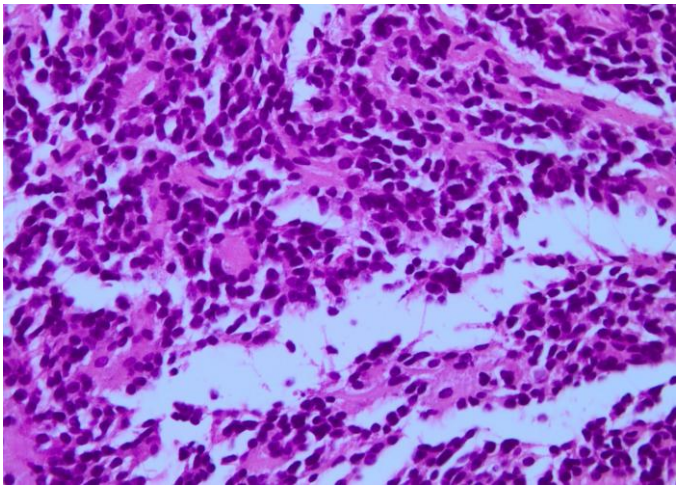


Fig. 5 - Medulloblastoma (WHO grade IV) classic variant , histology composed of densely packed cells with round to oval hyperchromatic nuclei surrounded by scanty cytoplasm. Area with Homer Wright rosettes (H & E stain x 20).

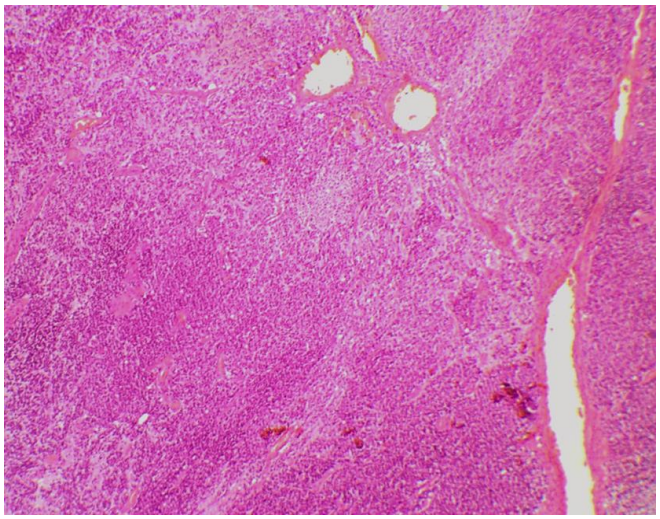


Fig. 6 - Medulloblastoma (WHO grade IV), desmoplastic/nodular variant (HE x 10).

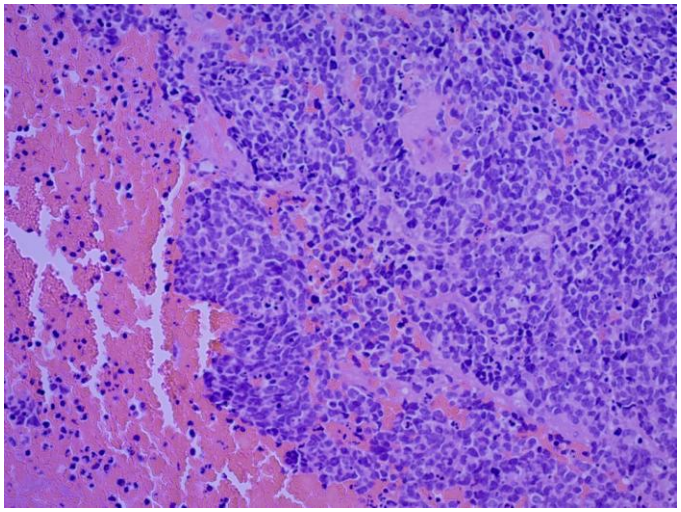
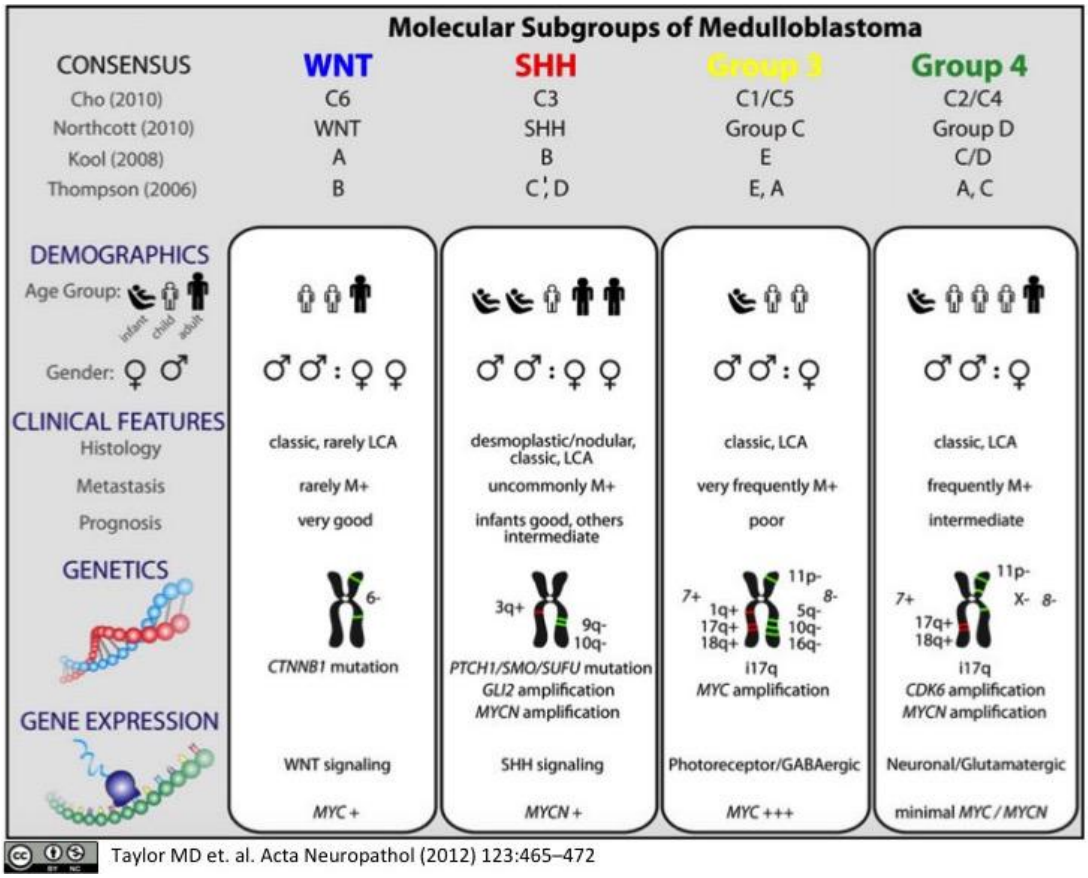


Fig. 7 - Medulloblastoma (WHO grade IV) anaplastic/ large cells variant (HE x 20).

Through the use of integrated genomics, at least four molecular variants of medulloblastoma have been described and identified. The importance of this classification is that each group has a unique transcriptional and genetic profile which creates clinically distinct presentations.[2]

The four molecular subgroups are termed WNT, sonic hedgehog (SHH group), group 3, and group 4.[17-19] These subgroups have significant prognostic value that is independent of the presence of metastases or unfavourable histology. The WNT subgroup is characterised by activation of the WNT pathway, and tumors commonly harbor mutations in the beta-catenin gene (CTNNB1).

These tumors primarily occur outside the infant age group and tend to carry a favourable prognosis with rare occurrence of metastases. The SHH sub group is characterized by activation of the SHH pathway and is more common in infants with desmoplastic tumors and in adults; however, it can occur in all age groups and is associated with all histological variants. Prognosis tends to be good for infants and intermediate for others. Group 3 medulloblastomas have a poor prognosis and are commonly associated with metastatic disease. Infants and children are the primarily affected populations. MYC amplification is common in group 3 medulloblastomas, and the survival rate in these patients is dismal. Group 4 tumors have an intermediate prognosis and are associated with isochromosome 17q and MYCN amplification. All age groups are affected and metastases frequently occur. (Fig.8)



Taylor MD et. al. Acta Neuropathol (2012) 123:465–472

Fig. 8

Staging

The staging of medulloblastoma is based on the modified Chang's staging system. Patients are risk stratified into either an average risk group or high risk group based on the tumor stage, patient's age, and the extent of any previous surgical resection.[20]

T1	Tumor <3 cm in diameter
T2	Tumor >3 cm in diameter
T3a	Tumor >3 cm in diameter with extension
T3b	Tumor >3 cm in diameter with unequivocal extension into the brainstem
T4	Tumor >3 cm in diameter with extension up past the aqueduct of Sylvius and/or down past the foramen magnum (ie. Beyond the posterior fossa)
M0	No evidence of subarachnoid or hematogenous metastasis
M1	Tumor cells found in cerebrospinal fluid
M2	Intracranial tumor beyond primary site
M3	Gross nodular seeding in spinal subarachnoid space
M4	Metastasis outside the cerebrospinal axis (especially to bone marrow, bone)

Children older than age 3 are categorised as having average-risk or high-risk diseases based on the Chang staging system. The prognosis of patients with metastases does not differ for M1, M2, and M3. All patients older than the age of 3 years with no evidence of disseminated diseases and residual tumor at the primary site of less than 1.5 cm^2 are classified as having average-risk medulloblastoma. All patients younger than age 3 are designated as high-risk. Patients older than age 3 with average risk diseases have a 5-year survival rate of 85% with combined chemotherapy and reduced-dose radiotherapy, and patients older than age 3 with high-risk disease have a 5 year survival rate of 70% with combined chemotherapy and high-dose radiation therapy. In children younger than 3, histology is predictive of outcome.

5. TREATMENT

5.1. Surgical

The most common initial treatment for medulloblastoma is gross total resection of the primary posterior fossa mass through a suboccipital craniotomy. The aim of surgical resection is to completely remove the entire tumor or, if this is not possible, to resect as much of the tumor as is safely possible.
The craniotomy is preformed with the patient in the prone position and the neck flexed. Initially superficial tissues and muscles are dissected, and a portion of the occipital bone and the laminae of C1 are removed. The dura covering the cerebellum is then opened, and the two hemispheres are retracted through either the split vermis or a telovelar approach. At the beginning of surgery it is important to visualize the floor of the 4^{th} ventricle to confirm that the resection is not carried into the brainstem, even though this tumor rarely invades the floor. If the surgeon resects a tumor that invades the brainstem, severe cranial nerve palsies can result, and this is never indicated because the tumor is sensitive to both chemotherapy and radiation, and residual brainstem disease likely does not significantly alter the outcome.[21] The use of intraoperative brainstem auditory evoked potentials can be considered if the tumor invades the cerebellopontine angle. Particularly in young children, care should be taken to prevent blood loss, as medulloblastomas can be fairly vascular, leading to considerable hemorrhage intraoperatively. Closing of the dura should be achieved in a watertight manner and the bone replaced after the procedure has been preformed. Within 72 hours of surgery a post operative MRI should be preformed to determine the extent of the resection as well to avoid obscuration by blood products and gliosis. A poorer outcome is possibly associated with residual disease over 1.5 cm^2, and repeated resection for a large residual tumor should be considered unless the surgeon stopped the initial resection because of excessive vascularity or invasion of critical structures.

5.2. Complications

The most common postoperative complication is the posterior fossa syndrome, also referred to as cerebellar mutism or cerebellar affective syndrome. A study showed that approximately 22% of patient developed posterior fossa syndrome postoperatively, however these cases were rated as moderate to severe, suggesting that the incidence of milder cases maybe much higher.[22] The symptoms typically manifest 24-48 hours postoperatively.[23] This syndrome is characterized by a triad of (1) decreased production of speech or mutism, (2) to cerebellar dysfunction including ataxia and axial hypotonia, and (3) neurobehavioural affective symptoms such as emotional liability, irritability, and apathy.[24,25] Nonverbal children are typically inconsolable with sharp, high pitched wining and display marked apathy with a lack of initiation and hypokinesis. In up to 60% of patients fecal and urinary incontinence have been observed. The pathophysiology is not completely known and is beyond the scope of this paper. There is recent evidence of presurgical language impairment as the primary risk factor for the development of the posterior fossa syndrome; children without a presurgical language deficit did not develop mutism, suggesting that the technical aspects of surgery are unlikely to be causative.[26] Conclusive of this information is that surgical approaches that avoid splitting the cerebellar vermis do not seem to prevent the development of this syndrome. The outcome of posterior fossa syndrome is variable. Classically children recover from mutism within 8 weeks, although residual ataxic dysarthria is common. 95% of patients with moderate or severe mutism one year postoperatively had speech impairments.[22] Other known neuropsychiatric deficits noted in patients with this syndrome, are deficits in receptive language, memory impairment, cognitive function, and executive function, indicating that multidisciplinary rehabilitation is required in these patients.[22,25] There are no available methods for either the prevention or treatment of posterior fossa

syndrome that have been shown to be effective beyond the level of anecdotal reports.

5.3. Non-Surgical Treatment

RADIATION THERAPY

Patients older than three years of age with an average risk disease are treated with a reduced dose (2,340 cGy) craniospinal irradiation, with a boost to the tumor bed or posterior fossa of 5,400 to 5,580 Gy after surgical resection of the primary tumor.[17,18] Following radiation therapy and adjuvant cisplatin based chemotherapy in patients with average risk disease results in survivals rates of approximately 85%. Patients who have high risk disease are treated with 3,600 cGy of craniospinal irradiation, with a boost to the tumor bed and to focal metastases followed by adjuvant chemotherapy, leading to a survival rate of approximately 70%. Delaying radiotherapy for more then 28 days postoperatively has negative prognostic impact.[27] Several adverse effects are associated with radiation therapy, predominantly cognitive impairment in younger children. Frequently observed side effects of radiation therapy are autotoxicity, thyroid dysfunction, growth failure, and radiation necrosis, which are inversely correlated with age. Children younger than age 3 have devastating cognitive outcomes when receiving irradiation and due to this protocols using chemotherapy alone are preferred despite inferior outcomes.[28]

CHEMOTHERAPY

Chemotherapy is included in current therapy for all patients with medulloblastoma. Children under the age of 3 even in disseminated cases are treated with chemotherapy only approaches. Three approaches have been studied for infant medulloblastoma, including systemic induction chemotherapy, followed by myeloablative chemotherapy with autologous stem cell support, followed by a radiotherapy for local relapse, combined systemic and

intraventricular chemotherapy, and systemic therapy with conformal local radiotherapy.[29] Five year survival rates of approximately 50-70% are accepted in all three of these approaches, with the desmoplastic variant having survivals close to 90%.[29] The intraventricular methotrexate approach requires the placement of a catheter or a shunt and adequate CSF flow. Methotrexate should not be given through a ventriculoperitoneal shunt without a device for transient occlusion to prevent drug induced peritonitis. Also, intraventricular methotrexate is associated with a dose dependent leukoencephalopathy of varying severity, and patients are at risk for radiation necrosis if they are also undergoing radiation therapy. A high risk for developing significant cognitive deficits (measures of intelligence and memory), is seen in young children treated with intrathecal methotrexate. Patients older than age 3 with average risk disease are treated with 4-9 cycles of combination post irradiation adjuvant chemotherapy which is usually cisplatin based. In patient with high risk disease a variety of approaches have been used to treat medulloblastoma, ultimately all of these approaches administer adjuvant chemotherapy following high dose craniospinal irradiation, leading to 5 year survival rates of approximately 70%.[30] Chemotherapeutic options are limited for recurrent disease, particularly in children with prior irradiation. A possibility is the use of high dose chemotherapy with autologous stem cell support with or without repeated irradiation, which can result in long term survival in 10-25 % of patients.[31] Although studies suggest that the outcome is favorable only in those patients with no evidence of disease or minimal residual disease at the time of high dose chemotherapy.

6. PROGNOSIS

Although the clinical criteria used to assign prognostic outcomes to the different risk groups continue to evolve, three features are currently used: metastases at presentation, the extent of postoperative residual disease and age. Risk groups are defined as follows:

- Average risk disease-Patients older than 3 years, stage M0 and with less than 1.5cm^2 of residual tumor post operatively. The 5- year survival rate is currently 78%.
- Poor risk disease-Patients older than 3 years, stage M1-M4 and/or with more than 1.5cm^2 of residual tumor postoperatively. The 5-year survival rate is currently 30-55%. Patients with anaplastic tumors are also considered in this risk group.
- Patients with non-posterior fossa tumors that are morphologically similar to medulloblastoma (primitive neural ectodermal tumors) have a poor prognosis similar to that of patients with poor-risk medulloblastoma, regardless of dissemination.
- Patients under the age of 3 years are defined as infants. Unfortunately, the worst prognosis occurs with this group, regardless of M stage and extent of postoperative residual disease. The 5-year survival rate is approximately 30%. Metastatic disease further worsens the prognostic outlook.

Even with a good response to surgery and radiation, recurrence in adults is common and these often occur within 2 years after treatment.[32] Recurrences tend to occur at the primary site in the posterior fossa. The incidence of recurrence in the spinal canal and the supratentorial region seems to decrease with the use of adjuvant chemotherapy.

Collin's law, known as period of risk for recurrence (PRR), has been

discussed as a reliable outline for the prediction of recurrence or cure of embryonal tumors including medulloblastoma. The PRR is defined as the age at diagnosis plus 9 months of gestation (reference pubmed). According to Collin's law, a patient who has no clinical evidence of recurrence within this time period is considered cured.[33]

More recently, histopathology and molecular subtyping studies have identified more specific groups for which survival ranges from excellent to very poor (1-4). How the histopathology and molecular grouping affects the use of radiation therapy remains to be determined.

7. CONCLUSION

Medulloblastoma is the most common malignant brain tumor in childhood, with proper diagnosis and treatment prognosis can be very favorable. The vast majority of medulloblastomas occur before the age of 16, and there is a bimodal peak of incidence between ages 3-4 years and 8-9 years, males are affected more frequently than females with a ratio of 1.4:1. Adult cases are unusual, accounting for less than 1% of braintumors. The tumor is rare beyond the fifth decade. Due to the location of medulloblastomas clinical signs and symptoms are usually related to hydrocephalus secondary to the obstruction of the fourth ventricle. The Initial diagnosis of medulloblastoma is usually made with noncontrast CT followed by MRI. The definitive diagnosis of medulloblastoma is made on microscopic pathologic examination, which also influences the treatment and prognosis of these patients. The most commonly used system of staging for medulloblastoma is the chang system which accounts for the size and the invasiveness of the tumor. the WHO classification system for medulloblastomas uses histology to classify medulloblastomas in to 3 major groups. Current treatment strategies for medulloblastoma are developed based on the risk stratification and the age of the patient. In all subgropus of patients, surgery is the first line treatment, which aims for maximal tumor resection. Postsurgical treatment further varies between higher risk groups and low risk groups receiving different combinations of chemotherapy and radiotherapy. Prognosis is greatly influenced by a combination of factors with an overall 5 years survival rate currently around 60%.

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10. BIOGRAPHY

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