

Childhood Medulloblastoma: Old Challenges, New Perspectives

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Medulloblastoma (MB) is the first primary central nervous system cancer of infancy. During the last thirty years, there has been an evolution of its treatment: although chemotherapy and radiotherapy have improved the prognosis, surgery remains a determinant key-factor for therapeutic outcome. The search of an effective adjuvant treatment along with a reduced toxicity is difficult. Following treatment with surgery, chemotherapy and radiotherapy, the prognosis for infants and young children with MB is still unfavourable and burdened by an high risk of neurocognitive deficits. The biological features of MB are not fully characterized, but now there are important directions for research. Clinical and molecular prognostic markers can be used to create a disease risk classification. In our review we resume the main features of MB, including clinical, histopathologic and molecular aspects and discuss on the therapeutic options for its treatment.

Keywords: Children; Histopathology; Infants, Moleculars; Medulloblastoma; Marker; Radiotherapy; Risk groups; treatment.

Medulloblastoma (MB) is the first primary malignant tumor of central nervous system during infancy. MB arises in the posterior fossa, specifically in cerebellum with metastasis via cerebro-spinal fluid (CSF) and this invasive embryonal tumor has specific manifestation in children as neuronal differentiation.

About 75% of MB comes up in cerebellum's vermis and throws itself into the fourth ventricle. High age of the patient and desmoplastic variant are related to an increased involvement of cerebellar hemispheres. Medulloblastomas often grow to several centimeters and may fill the posterior fossa, invading surrounding central nervous system (CNS) structures as they occupy the regional subarachnoid and ventricular spaces. The reported

frequency of CNS metastases at diagnosis is 11% to 43%, and such spread eventually occurs in as many as 93% of patients who come to necropsy.^{1,2} Among the paediatric CNS tumors, MB has the major ability of determining extraneural metastasis, especially in bone, liver, bone marrow, lung and lymph nodes.

According to some authors, cancers histologically not different from MB are PNETs (primitive neuro-ectodermal tumors) and they can be classified on their location.³ MB biologically is a single typology of tumor, and the last World Health Organisation (WHO) tumor's classification defines MB as a different class of embryonal tumor, divided from PNETs, pineal parenchymal tumors (with the inclusion of pinealoblastomas) and

ependymoblastomas.⁴ Magnetic resonance imaging (MRI) is a valid instrument for diagnosis and evaluation of disease's extension: in fact, staging studies, management protocols and treatment plans are based on disease stratification made by MRI.⁵

MB treatments are changed in the past three decades; it has been observed that combined protocols with chemotherapy and radiotherapy have an efficacy in >80% of the cases (especially when the disease is localised at diagnosis) against radiotherapy alone (efficacy in about 50% of the cases)^{5, 6} But, treatment are not free from long-term side-effects, in particular neurocognitive dysfunctions, especially for children of young age.⁷

Epidemiology

MB represents approximately 16% of all paediatric primary CNS tumors and no more than 1% of all adult primary CNS tumors.^{8,9} In infancy, MB presents two peak of distribution: the first between 3 and 4 years-old and the second between 8 and 9 years-old. In most cases, the aetiology of MB remains still unknown.

Genetic

Cancers arise as a result of mutations of genes that regulate cell proliferation and death. Gene mutation may originate within the germline or may occur as somatic mutations exclusively within tumor cells. Only a small fraction of children with brain tumors have germline mutations. Although the causes of the somatic mutations underlying the vast majority of all brain tumors are unknown, the genetic abnormalities typically associated with childhood brain tumors are being characterized through a growing body of evidence. Chromosomal anomalies have been defined further through molecular genetic analyses, including fluorescence in situ hybridization, studies of loss of heterozygosity and comparative genomic hybridization.

Deletions of chromosome 17's short arm (17p) distal to TP53 locus occur in 30% to 50% of medulloblastomas.^{10,11} Loss of 17p frequently occurs in association with duplication of 17q, which is characteristic of isochromosome 17q, the most common cytogenetic abnormality of MB.^{12,13} Deletions or mutations of chromosome 9q involving the Sonic Hedgehog receptor PTCH have been found in association with approximately 10% to 15% of sporadic MB.¹⁴⁻¹⁷ Fewer than 5% of

children with MB have inherited disorders.¹⁸ The most common of these are Turcot syndrome and the Gorlin syndrome (also known as "nevoid basal cell carcinoma syndrome").^{19,20}

Sonic Hedgehog receptor PTCH's germline alterations cause the nevoid basal cell carcinoma syndrome.²¹⁻²³ Children affected have a 3% incidence of MB and the age of diagnosis is anticipated respect to children without Gorlin syndrome. Children with Turcot syndrome, a disorder with dominant autosomic heredity, determined by adenomatosis polyposis coli (APC) gene's mutation or to different DNA mismatch repair genes (hPMS2 and hMLH1, for example),²⁴ have a high incidence of colorectal adenomas, gliomas and medulloblastomas. Multiple cancer types occur in children with Li-Fraumeni syndrome, determined by germline mutation of the TP53 gene^{25,26} Children with inherited mutations of TP53 gene most commonly develop low- or high-grade gliomas that may be multifocal, medulloblastomas, PNETs, and choroid plexus tumors.

Pathology

MB appears macroscopically friable, soft and highly cellular formed by basophil cells of different shape and size, reduced quantity of cytoplasm and, frequently, an elevated degree of mitoses. Homer Wright rosettes and pseudorosettes are variably present. Different stages of neuronal or glial differentiation are highlighted, demonstrating that tumoral origin cell is able to bipotential differentiation.

There are different histopathological patterns of this tumor

Classic MB: is formed by densely packed cells with round-to-oval or carrot-shaped highly hyperchromatic nuclei enclosed by scanty cytoplasm. Neuroblastic rosettes are distinctive but not constant peculiarity; a rosette is a circular disposition of tumor cell nuclei around cytoplasmatic processes, often characterized by specific nuclear polymorphism and elevated degree of mitosis. Apoptosis is more present than areas of necrosis.

Desmoplastic MB: this lesion shows nodular, reticulin-free zones (pale island) enclosed by densely packed cells with an elevated degree of proliferation which generate a dense intercellular

reticulin fiber network.²⁸⁻³⁰ Nodules are hypocellular with a rarified fibrillar matrix and a noticeable nuclear uniformity;

MB with vast nodularity and extensive neuronal differentiation: presents nuclear uniformity and cell streaming in a fine fibrillary background. This typology of MB, now and then, can change into a more-differentiated ganglion cell tumors,³¹ representing in this way a pathogenetically distinct group.³² In neuroimaging extreme lobularity is described with a “grape-like” aspect; large cells/anaplastic MB: this variant occurs in 4% of cases.^{33,34} Tumor cells are characterized by big, circular and/or pleomorphic nuclei with conspicuous nucleoli and a more plentiful cytoplasm. Necrosis is often present with elevated degree. Mitosis and apoptosis are both elevated. This type is similar to cerebellum’s rhabdoid/atypical teratoid tumours, except for immunophenotype and cytogenetics.³⁴

Synaptophysin is a characteristic feature of MB and most elevated in nodules and in the centers of neuroblastic rosettes.³⁵⁻³⁷ The majority of MBs contain stellate GFAP positive cells. Intermediate filament proteins have also been used to identify cell lineages in MBs.

Neuroimaging

Computed-tomography (CT) or MRI are valid diagnostic instrument in childhood MB. On CT this tumor appears well-defined, homogeneous and in the midline and it can be isodense or hyperdense in relation to cerebellar cortex.³⁸

When children begin older, MB’s pathways is characterized by the involvement of cerebellopontine angles and cerebellar hemispheres. Non-contrast CT evidences calcification in 10% to 20% of patients while necrotic or cystic areas are more incident.^{39, 40} Three pathways are evidenced after contrast enhancement: homogeneous enhancement (the most incident), heterogeneous enhancement and non-enhancement in 5-10% of the patient. MRI shows MB as a midline inferior vermian lesion, which completely interests fourth ventricle and which can arrive into the ventricular foramina.⁴¹ MB are usually low-to-intermediate signal on short time to relaxation/time to echo (TR/TE) images and isointense or slightly hyperintense on long TR/TE images.⁴²

Contrast-enhanced T1-weighted images demonstrate metastasis all over the subarachnoid

space, but a better resolution of this disseminations there is in gadolinium-enhanced T1 weighted images.⁴³

Neuroimaging of the entire neuraxis before the beginning of treatment is very important considering the high incidence of metastasis at diagnosis.

Clinical presentation

Presentation of brain tumors relates mostly to the site of tumor origin, children’s age, and their developmental level, but sometimes depends also on the tumor type. Symptoms of MB generally occur three months before diagnosis and they can be subtle and intermittent. Early cerebellar symptoms can be of difficult interpretation, such as: slow or hesitant speech, awkwardness, deterioration of handwriting and difficulty in hopping and running.

Tumor arising in the cerebellar hemispheres more commonly cause lateralizing signs, such as appendicular dysmetria and nystagmus, whereas midline cerebellar’s interest determines truncal instability, wryneck or augmented intracranial pressure. The clinical manifestations of MB also include: truncal ataxia, lethargy, disturbed gait, morning vomiting, intracranial hypertension secondary and headache.

Intracranial hypertension is caused directly by compression or infiltration of CNS or indirectly by the obstruction of cerebrospinal fluid circulation with consequent non-communicating hydrocephalus. Among school-aged children, deterioration of scholastic results, personality changes, fatigue and vague intermittent headaches are common. Papilledema may occur if the pressure is long standing. In infants and young children chronically increased pressure may lead to macrocephaly or cranial sutures’s removal. Tonsillar involvement or the upcoming herniation are preceded by stiff neck or head tilt.

Risk groups

Some of the clinical or biologic features of MB have prognostic value. Prognostic stratification in risk groups is very important for the tumor control. In addition, this stratification is very helpful for prognosis and therapy of MB. There are clinical and histological criteria to assign patients to a risk group.

Clinical criteria include

Age at diagnosis: younger age is

characterised by an elevated disease dissemination at diagnosed^{5, 44}; they have a lower rate of complete tumor resection⁴⁵ and less aggressive radiotherapy.⁴⁶ In addition, more aggressive histologic subtypes of MB34 occur more commonly in the first few years of life;

Extent of resection: a near-total resection (generally defined as a more than 90%) can be achieved in approximately 80% of medulloblastomas using contemporary microsurgical techniques.⁴⁷ According to Jenkin *et al.* gross total resection is characterized by a 5-years PFS of 93% in contrast with the PFS of 45% after incomplete resection.⁴⁸ The CCG study 921 highlights a connexion between resection's degree and outcome in patients without tumor dissemination.⁴⁹ The same study found that a disease's residue less than 1.5 cm² on imaging after surgical treatment was associated significantly with a higher PFS rate in patients with M0 disease; this effect was greatest in children older than 3;

Tumor size and extent: MB has an inherent tendency to metastasize; at diagnosis one-third of patients present metastases. The Chang staging system is used to assign stages of primary (T stage) and metastatic (M stage) disease (Table 1).

Treatment

Surgery with subsequent craniospinal radiotherapy with or without chemotherapy is the most used approach to MB. Chemotherapy is used since 1990s to reduce the use of radiotherapy and its CNS effects with an improvement of intellectual outcomes in children with brain tumors.^{45, 50, 51}

Surgery, radiotherapy and chemotherapy have different role in MB's treatment. Surgery's purpose is the complete resection of primary mass. Conditions which can prevent total resection are: brainstem involvement (the floor of the fourth ventricle is the most interested), metastasis of leptomeninges and subarachnoid spaces, and a widespread supratentorial involvement.

Tumor is reached through a suboccipital craniotomy or craniectomy with the children in prone or modified prone position. In patients with hydrocephalus, treatment with dexamethasone to reduce peritumoral oedema gives good results. If mental status is very injured, it is necessary a CSF diversion through a ventriculostomy, which will be removed in postoperative period.

Because approximately 10% of patients develop a postoperative syndrome of pseudobulbar symptoms and mutism (the "posterior fossa syndrome") after vermian tumor resections^{52,53}

Table 1. Chang staging system for posterior *fossa medulloblastoma*

Stage Tumor	Definition
T1	Cancer with diameter <3 cm and restricted in the midline of the vermis, the roof of the fourth ventricle and, less often, to the hemispheres of cerebellum.
T2	Cancer with diameter >3 cm, further diffusion in one of the next structure or in part in the fourth ventricle.
T3	Divided in T3a e T3b.
T3a	Cancer with diffusion in two of the next structures or completely in the fourth ventricle with involvement of foramen of Luschka, foramen of Magendie or the aqueduct of Sylvius. The consequence is an internal hydrocephalus.
T3b	Cancer involves the floor of the fourth ventricle or brainstem and filling the fourth ventricle.
T4	Cancer further crosses through the aqueduct of Sylvius to involve the third ventricle or midbrain, or cancer arises to the upper cervical cord.
Metastases	
M0	Absence of evident subarachnoid or hematogeneous metastasis.
M1	Microscopic tumor cells present in cerebrospinal fluid.
M2	Evident nodule seedings found in the cerebellar, cerebral subarachnoid space or in the third or lateral ventricles.
M3	Evident nodule seedings in the spinal subarachnoid space.
M4	Extraneural metastases.

(a reaction possibly related in part to the extent of the vermis incision) an attempt is made to incise only as much vermis as is needed to provide adequate exposure of the tumor.

MB is a relatively chemosensitive tumor. The most commonly used agent are classic alkylators and platinum complexes.⁵⁴⁻⁵⁶ New agent that are more effective and less toxic are needed. With regard to increasing disease control, chemotherapy has been employed in both neoadjuvant and adjuvant settings. In patients with tumoral residues or metastasis, chemotherapy offer potential advantages of treating micrometastatic disease throughout the CNS; of decreasing gross residual tumor before conventional radiotherapy of identifying active agents. The goal of adding chemotherapy to low-risk disease is to allow a safe reduction of radiation dose outside the posterior fossa so as to decrease the risk of late, adverse neurocognitive effects due to radiation.⁵⁷⁻⁶⁰ The International Society of Paediatric Oncology (SIOP) and the Children's Cancer Group (CCG) proved first the advantages of chemotherapy in newly diagnosed high-risk MB.

The trial analysed two different treatments: radiotherapy (36 Gy cranio-spinal irradiation and a boost to the posterior fossa to 54 to 56 Gy) followed or not by adjuvant chemotherapy.

CCG's regimen was based on vincristine contemporary with radiation followed by adjuvant vincristine, prednisone, and CCNU. SIOP regimen is resembling without prednisone.

Both trials highlight an important benefit from adjuvant chemotherapy, especially in the case of tumor of elevated degree.

Radiotherapy is generally adopted following surgery. MB is radiosensitive tumor; for decades, the standard curative therapy for MB has been craniospinal irradiation plus boost to the posterior fossa. In children > 3 years-old, it is administered 36 Gy of craniospinal irradiation for all neuroaxis and 54-59,6 Gy for posterior fossa.

In children treated with < 45 Gy to the local tumor site has been reported a major incidence of relapse.⁶³

Attempts at not irradiating the entire neuroaxis or omitting radiotherapy altogether have resulted in compromised survival.⁶² Conversely, craniospinal irradiation can produce intellectual and endocrinologic morbidity, most marked in younger patients. For these reasons the possibility of treating infants with standard risk MB chemotherapy alone has been explored.

Good results with adjuvant chemotherapy alone in young patients without metastases are highlighted by Rutkowski *et al.*, who reported also

Table 2. 2016 World Health Organization (WHO) Histological Classification of Medulloblastoma

WHO classification subgroup	Histology subtype	Prognosis and demographic notes
Medulloblastoma, WNT-activated	Classic	Low risk
	Large cell/anaplastic (very rare)	Uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53 mutant	Classic (rare)	High risk
	Large cell/anaplastic	High risk; incident in 7–17 years range
	Desmoplastic/nodular (very rare)	Uncertain clinicopathological significance
Medulloblastoma, SHH-activated, TP53 wild type	Classic	Standard risk
	Large cell/anaplastic	Unclear clinicopathological significance
	Desmoplastic/nodular	Low risk in infants; prevalent in infants and adults
	Extensive nodularity	Low risk in infants
Medulloblastoma, non-WNT/non-SHH, group 3	Classic	Standard risk
	Large cell/anaplastic	Elevated risk
Medulloblastoma, non-WNT/non-SHH, group 4	Classic	Standard risk
	Large cell/anaplastic (rare)	Unclear clinicopathological significance

as the Quotient-Intellective post-treatment was in normal range, but reduced when compared to children without tumor and better than of children in the trial who underwent radiotherapy alone.⁶⁴

Grill *et al.* reported as standard chemotherapy alone is able to increase the prognosis in patients without metastatic disease and with gross total resection, but not in presence of metastasis and incomplete resection.

In presence of local relapse, salvage treatment and re-radiotherapy of posterior fossa represent a potential approach.⁶⁵

In the last decade, high-dose chemotherapy with autologous haematopoietic stem cells rescue has been evaluated as treatment for various paediatric brain tumors: busulfan-thiotepa and etoposide-thiotepa along with carboplatin or BCNU are the treatments mainly used. After encouraging results, high-dose chemotherapy represents now the salvage or consolidation therapy in MB. High-dose chemotherapy supports brain distribution of hemotherapeutic drugs, which are unable to cross blood-barrier at conventional dosages.

Children with relapsed MB can benefit from temozolomide alone or in combination with etoposide treatment.⁶⁶⁻⁶⁸

Prognosis

MB is characterized by a poor prognosis and survivors are loaded by long term sequelae such as intellectual impairment, hearing loss, endocrinological deficits.

The overall survival (OS) at 5 years in patients > 3 years of age at the time of diagnosis with non-metastatic tumor is reported to be between 60% and 75% in different studies^{69,70}, whereas the survival for patients with metastasis at diagnosis is significantly poor, characterized by an OS at 5 years of 40%.⁷¹

In infants, prognosis is poorer probably due to the different biology of the tumor and to the radiotherapy limitations. OS at 5 years for patients < 3 years of age at the time of diagnosis with standard risk MB is 75%.^{57,58} Infants with metastatic disease have a dismal prognosis with an OS at 5 years of 15%-38%.^{64,65}

Infants

The definition of infant is imprecise and the elevated incidence of radiotherapy long term adverse effects on the developing CNS has

determined the use for mature children of treatment initially destined for infants.

The risk of developing CNS injury is more elevated in young age. The passage from tumor's destruction and irreparable nervous damage in infants and young children is rapid. During the second trimester, CNS catches up with adult neuronal numbers and this is followed by axonal and dendritic development.

However, brain continues his development during the 3rd or 4th postnatal year.⁷² For this reason, radiotherapy should be avoided or delayed in this subset of patients.

Intelligence quotient scores is the reference to evaluate treatment-related alterations in cognitive development.

Different risk factors are involved in Quotient Intelligence reduction, in particular treatment of long duration, female sex, younger age at time of treatment, hydrocephalus, radiotherapy and its dose and the volume of the brain irradiated.^{73,74} There are also an impact on functional outcomes, such as: ototoxicity, marital status, speech, visual acuity, endocrinopathies, vision, type education, hearing, deambulation and dexterity, living arrangements.⁷⁵⁻⁷⁷ The risk of such damages is high particularly in children treated aggressively and younger.

Medulloblastoma and molecular markers

In the last years, results have been obtained about the knowledge of the molecular genetic alterations which are at the basis of the genesis and development of embryonal tumors. Signalling systems, which support physiological cerebellum's growing, is very interested by the molecular genetic alterations. About specific gene disregulation have been studied some alteration in transduction in MB.

The wingless (WNT) signalling is involved in regulating cell proliferation. Dysregulation of this pathway is a significant cause in oncogenesis. About 15% of sporadic medulloblastomas are determined by proteins' mutations on the WNT signalling pathway.

The mutation of APC gene, present in a subgroup of children with Turcot syndrome (characterized by the contemporary presence of colon and brain cancer), predisposes to the development of MB.^{78,79}

The Sonic Hedgehog (SHH) pathway is fundamental in cellular proliferation and differentiation and also in cerebellar growth.⁸⁰⁻⁸², 83 This pathway is also involved in the genesis of sporadic and hereditary MB.

The evidence of PTCH mutation in Gorlin's syndrome (characterized by a major risk of basal-cell carcinoma and MB) prompts also the involvement of PTCH dysregulation in Sonic Hedgehog pathway in MB development.⁸⁴⁻⁸⁸ The Neurotrophin signalling pathway supports neuronal growing, differentiation and surviving.⁸⁹⁻⁹¹

It is also implicated in cerebellar development. Neurotrophin family links with high affinity Trk receptors. Evaluation in MB cells *in vivo* and *in vitro* of neurotrophin pathway and research of TrkC receptors' concentration in primary tumor samples underline as this pathway corresponds to a less malignant phenotype.⁹²⁻⁹⁶

ErbB receptor signalling transduction pathway is at the basis both cerebellar growing and MB genesis.

ErbB2 receptors is fundamental in this pathway: in fact, signalling by these receptors results in increased cell proliferation, invasion and migration^{97, 98} and these qualities account for its elevated oncogenicity.

In the fourth edition of the WHO Classification of Tumors of the Central Nervous System, the international consensus' definition of these subgroups has been utilised as basis of diagnostic criteria by WHO.^{99, 100}

WHO classification comprises molecular subgroups, which allow patient's prognostic evaluation and put the basis for clinical trials finalized to the research of new targeted therapies (Table 2).

CONCLUSIONS

The improvement of neurosurgical techniques, the redefinition of dose and delivery of radiotherapy and the optimization of chemotherapy have determined an increase of survival of children affected by MB.

However, larger and new studies are needed in order to further improve the prognosis of high-risk MB groups represented by infants and children with metastatic spread.

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