Pediatric Medulloblastomas

- Pathology -

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I. Introduction-Definition

Medulloblastoma (MB) is a Primitive Neuroectodermal Tumor (PNET) located in the Posterior Cranial Fossa (FCP). It is a malignant cerebellar tumor (WHO grade IV), with a predominant neuronal differentiation and a tendency to spread via cerebrospinal fluid (CSF) (37). It represents 40% of cerebellar tumors, 15% of all brain tumors and is the primary cause of malignant brain tumor in children (54). In France, an estimated number of 100 new cases are diagnosed yearly. The overall five years survival rate is about 75% to 80% in the absence of metastases. Metastasis is one of the main prognostic factors (5, 25). All the advances made with stratified analysis of the patients has led to few cases in each subgroups thus a need for an international collaboration to harmonize diagnostic and therapeutic strategies and long-term monitoring.

II. History

The term 'medulloblastoma' was originally introduced by Percival Bailey, who was working with Harvey Cushing: 'In 1925, I isolated a type of glioma which occurs chiefly in the center of the cerebellum of children for which I suggested the name medulloblastoma' (3). Thereafter, Harvey Cushing published a comprehensive study on this tumor entity (14). The term has remained till date. It is worth noting that for these authors, the MB is assumed to be a glial tumor, even though descriptions of histological preparations are very precise and similar to those currently performed. We invite readers interested in the history of MB to refer to the article by Rutka and Hoffman (59).

III. Natural History

The natural history of primitive neuroectodermal tumor remains debatable (4). These tumors, of the PCF, tend to infiltrate the fourth ventricle and sometimes the floor. MB can spread along the neuraxis in about one in three children and exceptionally outside the central nervous system (see following paragraphs). The tumor originates in the cerebellar vermis in 75% of cases (then invades the fourth ventricle); it is rarely located in the cerebellar hemispheres (37).

As with any CNS malignancy, the duration of symptoms before diagnosis is relatively short, compared to benign or low grade lesions. However, this duration can be variable for children with MB (6, 31, 70). In a large prospective study, the time to diagnosis ranged from 0 to 2 years, with a median of 2 months (23).

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IV. Epidemiology

The incidence of medulloblastoma is 5 to 10 cases per 1 million children corresponding to approximately 150 new cases per year in France. The annual incidence is estimated at 0.5 per 100 000 children under 15 years (66). The American epidemiological surveillance (SEER) reported a decrease in the incidence of medulloblastoma, while the incidence of supratentorial PNET is increasing (42).
Medulloblastoma is observed at any age but 75% of tumors occur in children with a median age of 9 (57). Boys are more often affected than girls (sex ratio 1.5: 1). These are mostly sporadic cases but some genetic predispositions are associated with medulloblastoma: Gorlin syndrome (Basal Cell Nevus Syndrome), Li-Fraumeni syndrome, Bean syndrome (cutaneous and gastrointestinal telangiectasia), Turcot syndrome, ataxia-telangiectasia, Rubinstein-Taybi syndrome or mutation SUFU (1, 9, 20). In a study of 82 cases of medulloblastoma, a predisposing syndrome was observed in 9.7% and 28% in children aged under 14 and 3 years respectively (9).

V. Pathophysiologic Principles Of The Disease Process

MB often present with hydrocephalus secondary to compression of the CSF pathway, then cerebellar damage (static and / or kinetic cerebellar syndrome) and / or meningeal metastatic dissemination. The following can also be observed: long track affection with gait disorders, oculomotor paralysis (VI cranial nerve), other cranial nerve deficits, nystagmus, speech difficulties....

Medulloblastoma is the intracerebral tumor with the greatest propensity to metastasize. In 30-35% of cases, it is found in the CNS in the form of nodules in the brain and / or neuraxis or neoplastic meningitis. Spinal involvement may present with back pain, signs of spinal cord compression or radiculopathy. The clinical signs of meningeal metastases are those of meningitis. Medulloblastoma is the only intracerebral tumor which metastasizes outside the CNS; the most common sites being: the bone and then the bone marrow and exceptionally the lymph nodes, liver or lungs. These metastases are very rare, representing less than 5% of cases (37, 38). Such presentations demand the need for an emergency brain MRI (and of the spines if possible) to make the diagnosis of a posterior fossa space occupying lesion and rule out hydrocephalus.

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VI. Diagnosis

1. Clinical Features

Symptoms related to intracranial hypertension in younger children include behavioral problems, irritability, decreased interactivity, hypotonia and vomiting. When the fontanelles are still open, increase in head circumference is the predominant feature and may be associated with a bulging anterior fontanelle and gapping of sutures. However the fundus examination may be normal because of the possibility of the skull to expansion. In older children, headache, especially in the morning, dominates the picture.

Other revealing signs may point to the tumor such as vomiting without nausea occurring mainly in the morning. The vomiting sometimes is misinterpreted as a symptom of digestive ailments especially among younger children. Diplopia can result from cranial nerve six compression due to hydrocephalus. Visual disturbances are much rarer and are due to papilledema.

These signs may precede those related to cerebellar dysfunction for a time period which rarely exceeds two months. At a more advanced stage of intracranial hypertension, torticollis can occur suggestive of herniation of cerebellar tonsils into the foramen magnum necessitating an emergency hospitalization in neurosurgical unit.
2. Imaging Features

They aim to detect hydrocephalus, to better characterize the lesion for surgical resection and to search for any CNS metastases.

Brain MRI with and without contrast injection is the examination of choice. It precis on tumor location (usually the vermis with extension to the fourth ventricle, sometimes hemispheric or cerebellar pontine angle), its dimensions and its effects on the size of the ventricle. Typically, the MB is a rounded compact mass, at the center of the posterior fossa, homogeneous, hypointense relative to the cerebellar cortex in T1, iso-or hyperintense on proton density, hyperintense in T2, moderately enhanced after contrast medium injection. This classic form is observed in about half of cases. (Figures 1-5 and Figure 7). The diagnosis is more difficult when the tumor is invasive, necrotic, hemorrhagic, poorly enhancing, or when it extends to cerebellopontine angles.

Figure 1. Medulloblastoma: typical appearance: large tumor developing mainly into the fourth ventricle (Mid-Sagittal MRI T2-Weighted images). Note the radiological herniation of the lesion into the foramen magnum.
Figure 2. Pediatric Medulloblastoma: typical appearance. (Axial MRI T2-weighted Image showing a large fourth ventricular lesion).
Figure 3. Tumor growth into or towards the fourth ventricle, heterogeneous, seemingly well demarcated, with small cysts. (Axial MRI T2-weighted images).
Figure 4. Medulloblastoma: heterogeneous tumoral lesion, located in the fourth ventricle, with discrete and heterogeneous enhancement after gadolinium injection (axial cut of contrasted T1-weighted MRI image).
Figure 5. Mid-Sagittal MRI T2-weighted Image: endoscopic ventriculostomy permeability (flow artifact visible in the floor of the third ventricle). Large posterior fossa tumor.
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Figure 7. Surgical emergency. Brain MRI: T2-weighted image Mid-Sagittal cut,. Voluminous posterior fossa lesion causing foramen magnum herniation and cranio-cervical junction compression.

The MRI sometimes allows for the appreciation of tumor infiltration of fourth ventricular, the brainstem, cerebellar peduncles and extension through the foramen of Lushka. It also enables detection of supratentorial and/or spinal metastases as well as meningeal dissemination in the form of contrast enhanced lesions of the arachnoid mater. MRI of the spinal axis should be complete, including the whole thecal sac. MRI is done preoperatively to avoid artifacts in the spine due to bleeding from surgery that can be mistaken for spinal "mets". (Figures 1-8).
Figure 6. MRI: Mid-sagittal gadolinium-enhanced T1-weighted image. Nodular metastases along the spinal axis.
Figure 8. Postoperative MRI with complete excision of the tumor.
3. Anatomopathologic Features (figure 11)

Diagnosis is based on histological examination of a non-necrotic tumor specimen. The diagnosis of medulloblastoma is made by the presence of small round or sometimes fusiform cells, which are very basophilic, with a high nucleo-cytoplasmic ratio, intense activity mitotic activity and sometimes arranged in the so called Homer-Wright rosettes or pseudorosettes, characterizing its neuroectodermal origin (24, 37).

The WHO 2007 classification (World Health Organization) places medulloblastoma under embryonic neuroepithelial tumors, and distinguishes them from other tumors of the same type located outside the cerebellum. Five histologic subtypes are distinguished (37):

- The **classic form** composed of cells with hyperchromatic nuclei, and with less than 40% of Homer-Wright pseudo-rosettes.
- The **desmoplastic / nodular type** characterized by an abundance of collagen fibers and reticulin. Nodules correspond to zones of neuronal maturation. It occurs primarily in very young children in the cerebellar vermis but can also occur also in adolescents and young adults with cerebellar hemispheric localization. The prognosis is very good for young children (60).
- Two aggressive forms called **anaplastic** (5% of cases) and **large cell** medulloblastoma (2-4% of cases) have many similar features, including cells with large round and / or pleomorphic nuclei, vast bands of necrosis, a high mitotic index and a large proportion of cells in apoptosis. Their prognosis is pejorative (8).
- Medulloblastoma with **extensive nodularity** that occurs mostly in very young children

Other much more rare varieties, have been described: the **medullomyoblastoma** and **melanotic medulloblastoma**.
VII. Treatment

The standard treatment is tumor resection, irradiation of the entire neuraxis except in children under 5 years old, and chemotherapy according to different modalities. So far, stratification into risk groups has been based on age and the presence of residual tumor and / or metastasis. The distinction of five histologic subtypes and the contribution of molecular biology has enabled the current definition of new paradigms for the multidisciplinary management of this disease (20). Finally, a better understanding of the molecular mechanisms underlying the development of the different types of medulloblastomas offers the prospect of targeted molecular therapies being tested in some patients with tumor relapse.

The classification used in most published series is that of Chang (12) based on a review of operative-records and autopsy performed since 45 years. This classification ought not to be used because of advances in imaging, the lack of impact of tumor size on survival (T) or differentiation between brain or spinal metastasis (M2 or M3). New classifications have been proposed (18), but none is currently the reference. The most important issue is to clearly precise on the quality of surgical excision by analyzing the operative report and MRI performed within 48 hours after excision.

Medulloblastomas are currently distinguished into 2 groups:

- 'Standard Risk' Medulloblastomas

Total or subtotal resection (no residual tumor identified on post-operative MRI, or tumor residue with surface area of <1.5 cm² on MRI axial cuts) or absence of supratentorial or spinal metastases; no meningeal spread ;

- 'High Risk' Medulloblastomas

Residual tumor> 1.5 cm² , and / or existence of supratentorial or spinal metastases and / or the presence of an invasion of the cerebrospinal fluid.

Molecular biology classification (Table I)

Table I. Classification of medulloblastomas using molecular biology (4 groups)

<table>
<thead>
<tr>
<th></th>
<th>Wnt (15%)</th>
<th>Shh (25%)</th>
<th>Groupe 3</th>
<th>Groupe 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Classic, rarely large cell / anaplastic</td>
<td>Classic, large cell / anaplastic, desmoplastic / nodular</td>
<td>Classic, large cell / anaplastic</td>
<td>Classic, large cell / anaplastic</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Rares</td>
<td>Less frequent</td>
<td>More Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Very good</td>
<td>Good in infants, intermediate in the aged</td>
<td>Poor</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Genes</td>
<td>Mutation of CTNNB1</td>
<td>Mutations of PTCH1/ Smo/ SUFU; amplification of Gli2; amplification of NMYC</td>
<td>amplification of MYC</td>
<td>Amplification of NMYC and CDK6</td>
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</table>
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Therapeutic management is also guided by the age of the child. For younger children, current studies seek to avoid or delay the CNS irradiation because of the deleterious effects of radiation on the developing nervous system (see below). The age limit below which the irradiation of the entire CNS is contraindicated depends on the results of ongoing studies; and is currently set at five years.

Preoperative workup includes ophthalmic examination to detect signs of intracranial hypertension (especially papilledema) and serves as a baseline for follow up.

1. Surgical Treatment

   - Principles

Treatment of hydrocephalus

Tumor resection cannot be performed in the presence of significant intracranial pressure observed in 60-80% of cases. Treatment of hydrocephalus must always be discussed. Treatment by endoscopic third ventriculostomy (ETV) is gradually replacing the external drain and ventriculo-peritoneal shunt. A CSF sampling should be routinely done for cytology if treatment of hydrocephalus is necessary.

Surgical Treatment

Surgery involves tumor resection from the posterior fossa and, if necessary, to treat hydrocephalus before this procedure. However, if there are clinical signs and/or significant radiological signs of herniation at the foramen magnum (Figure 7), surgical resection should be performed urgently, with an external ventricular drain inserted at the end of surgery (to avoid death from acute postoperative hydrocephalus).
Figure 7. Surgical emergency. Brain MRI: T2-weighted image Mid-Sagittal cut., Voluminous posterior fossa lesion causing foramen magnum herniation and cranio-cervical junction compression.
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The posterior fossa (PCF) approach used is not specific for MB surgery. Details wouldn't be discussed here, but apply to any midline PCF tumor. It is done in lateral decubitus or sitting position; the latter preferred by the authors. (Figures 9 and 10). Indeed, the authors observed fewer complications as in other series (50). However it is worth precising certain principles that must be kept in mind during this surgery:

- Special attention must be paid to the cerebellar vermis, as it plays an important role in the cognitive processes (41, 62) and vermian lesions are widely incriminated in subsequent neurocognitive sequelae (55). It is therefore appropriate to prefer the telo-velar approach (15, 46) to a vermian incision. This approach allows for a better exposure angle in all planes compared to the transvermian (except for the rostral part of the fourth ventricle, but the removal of the posterior arch of C1 optimizes the quality of exposure). In addition, in order to limit the deleterious compression on the dentate nuclei, we recommend using only one retractor, which in principle should be inclined on one or the other cerebellar tonsil to access the tumor.

Figure 9. Sitting position for posterior fossa surgery. Marking of incision Line (from the external occipital protuberance to the spinous process of C2).
The telo-velar approach requires the removal of the posterior arch of C1, which wouldn't affect the stability of the cervical spine, as long as the integrity of C1-C2 ligaments are respected

- The trans-vermian approach are to be avoided, if not proscribed.
- Results

Tumor excision should:

- Allow for the diagnosis of medulloblastoma
- Be as complete as possible (a residue < 1.5 cm² however is of little impact on prognosis)

Consequences (side effects, complications)

Complications of the PCF surgery are:

- Mutism
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- Posterior fossa Syndrome (its incidence is similar to that of cerebellar mutism and be prevented intraoperatively: see previous paragraph).

- CSF Leak

- Infections (local, abscesses, meningitis ...)

- Wound gapping

- Acute hydrocephalus

- Neurocognitive alterations (for affection of the fronto-cerebellar pathways) (65).

POST OPERATIVE WORKUP

It should be done in the immediate postoperative period, within 48-72 hours after surgery. MRI done after this period is of no value because it does not distinguish a residual tumor from post-operative bleeding or even a post-operative scar. It is aimed at detecting the residual tumor in the posterior fossa and should include MRI with and without contrast injection.

CSF examination from a lumbar puncture between the seventh and the fifteenth day after surgery aims at detecting subarachnoid dissemination by cytocentrifugation of CSF and measurement of the protein level.

MRI or CSF cytology alone does not completely rule out metastatic spread but these two investigations should be systematically done.

BIOLOGY AND MOLECULAR BIOLOGY

After tumor resection, some laboratory tests should be routinely done to stratify the disease and define the therapeutic strategy. Immunohistochemical examination may reveal ²-caténine which is of good prognostic value. (19).

Preservation of tumor samples in a tumor bank after freezing to - 80 ° C is essential to study the prognostic value of various biological parameters.

Molecular biological studies should investigate for the amplifications of C-Myc and N-Myc oncogenes that are of unfavorable prognosis and most often seen in the anaplastic / large cell types.

Furthermore, a detailed analysis by different methods of molecular biology has clarified the embryonic tumorigenesis of medulloblastomas to enable molecular classifications that have been developed over the years. Thus, the normal development of the cerebellum requires the activation of signaling pathways including sonic hedgehog pathway (Shh) and wingless (Wnt) (58) pathway. A mutation in these pathways results in the development of the Shh subtype of medulloblastoma, mainly located at the 4th ventricle and Wnt subtype type generally located in the cerebellar hemispheres. The current classification recognizes four risk subgroups (Wnt, Shh, Group 3 and Group 4) takes into consideration the demographic, clinical presentation, histology and genomic profile (47). These subgroups Shh, Wnt and non-Shh / Wnt respectively account for approximately 25%, 15% and 60% of medulloblastomas (61).
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The Shh subtype is mainly in children less than 3 years; its histology essentially corresponds to the nodular / desmoplastic form and the prognosis is good in infants, intermediate in older children.

In the Wnt subtype; classical histological form is common; it occurs at an older age; it rarely metastasize and prognosis is very good.

In group 3, the tumors are often metastatic, the histology is of the anaplastic or large cell type, and occurs in younger children with a masculine preponderance. The prognosis of this group is the most pejorative.

Group 4 involves mainly younger children; metastatic forms exist but are less frequently than in group 3, histology is essentially that of the classic type. The prognosis is intermediate.

The histologic differential diagnosis of medulloblastoma includes other posterior fossa tumors such as the ependymoma with a different histological appearance (perivascular arrangement of rosettes providing a fibrillar space network around the vessels) and especially the ependymoblastoma, another PNET arising from fourth ventricle and having an ependymal differentiation. The therapeutic management of these two primitive neuroectodermal tumors of the posterior fossa is currently the same.

2. Radiotherapy

Medulloblastoma is a highly radiosensitive tumor. The high propensity of medulloblastoma to spread across the CNS and the failures of radiation therapy focused to the posterior fossa have led to radiotherapy of the entire central nervous system. The latter is done using rigorous techniques in order to limit the risk of overdose to the cord and underdosing of the subarachnoid space. Conventionally 54 Gy is delivered in 30 fractions of 1.8 Gy to the tumor bed; from 25-36 Gy in 12-18 fractions of 1.8 Gy on the brain and the spinal axis.

Brain metastases can receive focal irradiation of 45-54 Gy (depending on the target volume); spinal metastases above L2 focal irradiation of 39.6 to 45 Gy (also depending on the target volume) and those below L2 focal irradiation of 50.4 to 54 Gy.

This should be done with extreme rigor and quality control including a review of centering layouts necessary for precise irradiation (10). New technologies such as tomotherapy facilitate the technique. Similarly, proton therapy, although still with limited access in France, are advantageous in the protection of the auditory apparatus. RT is done as soon as possible after surgery or after chemotherapy which can be intercalated ('sandwich' chemotherapy). In this case, the time between surgical excision and radiotherapy, defined in each protocol is in the order of about 90 days. The surgery-radiotherapy time interval and the duration of radiation therapy are essential prognostic factors. It has been shown in the SIOP II study comparing the cranio-spinal irradiation (CS) in which irradiation with 36 or 23,4Gy, is or is not preceded by chemotherapy that the results were worse for the group of patients who underwent a pre-radiotherapy chemotherapy due to a delay in radiotherapy (2).

If the hematologic profile has been altered by chemotherapy, then radiotherapy can start in the posterior fossa if there is no metastasis or meningeal dissemination to avoid hematotoxicity due to irradiation of the spinal axis.

In rare occasions, radiation therapy may cause a surge in intracranial hypertension, and / or exacerbate pre-existing neurological signs. This complication usually responds well to corticosteroids.

Sequela caused by the RT led to a change in the modalities for irradiation in the standard risk group. Reducing the
cranio-spinal dose to 23.4 Gy without chemotherapy has been the subject of several trials with conflicting results: no loss of opportunity in the SIOP II study (2), and excess spinal recurrences in the POG8631 / CCG923 study yet without significant difference in survival at eight years (67). However, in most studies, the association of low dose cranio-spinal irradiation to chemotherapy improves the prognosis with a five-year disease-free survival of 75 to 80% (51, 68).

A bi-fractionated radiotherapy was also tested in order to reduce the irradiation sequallae in the MSFOP 98 study that delivered a dose of 36 Gy to the cranio-spinal axis without associated chemotherapy. Overall survival at six years was 78% and progression-free survival of 75% (11). The results in terms of cognitive function are promising. In the randomized study of the International Society of Pediatric Oncology (SIOP) comparing hyperfractionated versus conventional radiotherapy followed by chemotherapy, there was no difference in event-free and overall survival nor in terms of auditory toxicity (40).

Toxicity of the auditory apparatus that occurs in about two thirds of cases appears between 50 and 60 Gy. Reducing the volume irradiated in the posterior fossa limits the toxicity. This was shown in a study comparing conventional radiation and intensity modulated RT (IMRT) in which 84% of patients treated conventionally had an auditory toxicity (64% grade 3-4) against 27% in the IMRT group (including 13% grade 3-4) (34). It has recently been shown that the use of proton therapy is also possible to reduce the frequency and severity of radiation-induced ototoxicity (43).

3. Chemotherapy

Medulloblastoma is the most chemosensitive CNS tumor after germ cell tumors as shown by the response rate observed in the residual tumor or recurrent forms (13). These rates vary between 60 and 90% according on the results of Phase II studies where the number of evaluable patients, was however, between ten and thirty. The best response rates were obtained with polychemotherapy with a platinum derivative. Combined chemo- and radiotherapy has increased survival rates and reduced the doses of prophylactic radiotherapy from 35-25 Gy in standard risk patients (51). In children less than 5 years it has also permitted to defer radiotherapy or avoid it in some low-risk patients (27, 59).

Successive clinical trials and advances in biology have enabled a distinction in treatment groups according to age of the child, the grade, the quality of excision and biology of medulloblastoma.

For children over 5 years of standard-risk group (localized, no tumor residue, not of unfavorable biology), the use of 8 cycles of poly chemotherapy with cisplatin CCNU and vincristine is currently the standard treatment after radiotherapy. This treatment gives a 5 years survival rate of about 85% (40).

There is no defined standard treatment for high-risk patients. Besides surgery and cranio-spinal irradiation, other treatment modalities include, conventional or increasingly high dose chemotherapy followed by autologous hematopoietic stem cells (HSC) transplantation. Encouraging results have been reported with a recurrence-free survival rate of 70% at 5 years (22).

With regard to children under 3 to 5 years of standard risk, several chemotherapy protocols have been tested to defer or even avoid irradiation. Most of these protocols use some or all of the following molecules: vincristine, cisplatin, carboplatin, etoposide, cyclophosphamide, and methotrexate.

In BBSFOP study, 22% of children were alive at 5 years with prolonged postoperative chemotherapy without radiotherapy. Five year progression-free survival was 41% in the R0M0 group with complete resection versus 0% in case of subtotal resection (27). In this group, most relapses occurred in the posterior fossa and were treated with
conventional chemotherapy and high-dose chemotherapy followed by transplantation of HSCs and eventually by resection and radiotherapy to posterior fossa only in case of local recurrence, to obtain an overall 5-year survival of 73%.

In the German HIT SKK study combining conventional chemotherapy, administration intraventricular methotrexate and systemic high dose methotrexate, event-free survival at 5 years was 83% (59). These studies clearly identify prognostic factors for medulloblastomas in children under 5 years, with worst prognostic factors being: histologic classic or anaplastic / large cells types, the existence of a residual tumor and metastases whereas the best survival rates were observed among the cases of medulloblastoma of desmoplastic / nodular or extensive nodularity types, localized tumors, without residue or metastasis (60). It has been shown, via remotely conducted neuropsychological tests that intellectual sequelae were significantly lower among children who had not received craniospinal irradiation.

In case of relapse or progression, it is possible to propose the inclusion in Phase II trials of metronomic chemotherapy with methotrexate-vinblastine-celecoxib-cyclophosphamide (CECS-Metro 01) or topotecan + temozolomide (TOTEM 2).

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Follow up

Follow up includes a clinical examination and completion of cranio-spinal MRI every four months during the first two years, every six months the following two years, and then once a year till five years (69). It is particularly important for younger patients treated with chemotherapy alone, as relapses can be effectively treated with chemotherapy and radiation (see above). In older children, aimed at improving the prognosis of relapses by earlier treatments whose effectiveness should be evaluated.

Sequallae

1. Neuro cognitives Sequellae

The different factors influencing the neuro cognitives sequelae are: the age at diagnosis, primary tumor (metastastastic potential, hydrocephalus), especially if late diagnosis, surgery (vermian incision) in case of complications, radiotherapy (whose effects are dose-dependent), chemotherapy, parental and school environment, and the quality of care of these sequelae.

The intellectual sequelae are much more pronounced if the age at diagnosis is early (45). Before diagnosis, intellectual sequelae can result from brain damage due to hydrocephalus, and can be more significant with late diagnosis. They can also the result from:

- trauma due to the placement of a CSF diversion device, surgery, the possibility of postoperative complications such as meningitis or shunt infection as the cerebellum plays a vital rule in the development of cognitive function. (32, 33, 36)
- Chemotherapy affection of the senses (deafness due to the use of platinum compounds) or related encephalopathy especially when combined with radiation (16, 17)
- Radiotherapy (28, 29) which is the leading cause of intellectual sequelae. Batteries of the various tests used enable the identification of abnormalities of attention, memory, coordination, speed fine motor, visual motor...
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process, mathematics and and spatial relations (35). The drop in IQ, though it does not fully reflect the intellectual adaptability, is the most commonly used parameter to report impaired intellectual performance (29).

- A decrease in IQ even if it does not fully reflect intellectual adaptability, is the most commonly used parameter to report impaired intellectual performance (29). It can occur in the first year following radiation therapy and continue over time, on average 5 to 10 years. Thus, in the study of Hoppe-Hirsh et al., as a result of radiotherapy at a prophylactic dose 35 Gy on the brain and a curative of 55 Gy for the posterior fossa, an IQ less than 80 is observed in 42 % and 85% respectively at 5 years and 10 years of diagnosis (32).

- Intellectual impairment is more significant when irradiation occurs early in life (45) which led to postponement of irradiation in children aged less than five years. In a study on the longitudinal follow of IQ, children older than 7 years at the time of irradiation had a significantly lower IQ at the end of study than for younger children and children with initial IQ higher than 100 were those whose with the greatest drop in IQ falls (56). Intellectual impairment varies directly with the volume and dose of irradiation (whole posterior versus tumor bed ) (29, 33, 64). Thus, in the study by Mulhern et al., Children who received prophylactic irradiation at a dose of 35 Gy had a lower average IQ score respectively of 8 and 10 percentage points compared to those who received the dose of 24 Gy (45). No correlation has been observed between the evolution of the IQ and the lesions that may appear on MRI (21).

2. Endocrine Sequellae

An impairment in the endocrine function is observed in more than 50% of cases. Impaired growth hormone secretion (GH) is the leading cause and the earliest of endocrine sequelae. Following irradiation of the hypothalamic-pituitary axis growth retardation can be detected at the third month (17). Abnormal response to GH stimulation test and / or a decrease in the growth rate can be observed at doses of 29 Gy or 18 Gy in the case of craniospinal irradiation (26). Combined chemotherapy is also implicated in the severity of short stature (49).

The occurrence of early puberty may pose the diagnostic problem of a normal growth velocity due to secretion of gonadotropins in children with impaired GH secretion which leads to a final decrease in height due to premature epiphyseal fusion. Treatment with GH is indicated there exists a complete deficit objectified by provocation tests. However, this treatment does not achieve a total recovery of height in all cases. Also, spinal irradiation causes a decrease in the growth of the spinal column independent of any anomaly of the GH due to the irradiation of the vertebral growth cartilage. This abnormal vertebral growth is more significant if irradiation occurred at an early age, and can lead to a deficit of 9 cm of height in the trunk (64). GH deficiency may also be responsible for changes in body composition and increased cardiovascular risk (30). The risk of increasing the incidence of tumor recurrence has so far not been reported (53).

Other neuroendocrine deficits may occur. The most common abnormality then is hypothyroidism which occurs in over half the cases related to the irradiation of the thyroid itself and the hypothalamic pituitary axis (30). Hypothyroidism is dose-dependent and can occur at a dose from 25 Gy to the neck. Due to the oncological risk of prolonged stimulation of the thyroid by TSH following thyroid irradiation, annual monitoring is necessary and an eventual treatment with thyroxine. Puberty may occur prematurely, due to prolonged hydrocephalus and especially from prophylactic brain irradiation (48); late occurrence is very rare and usually normally. Abnormalities of gonadotropins or cortico-adrenal axis are rare.

3. Neurosensorial Sequellae

The most common is a decrease in hearing related with the use of platinum compounds, but can also be due to radiotherapy. It is dose-dependent and is severe in about 10% of cases (39). Neurological sequelae are primarily cerebellar and tend to improve over time (52).
4. Quality of life

Very few studies have reported the quality of life of patients treated during their childhood for medulloblastoma. In the most documented study involving 342 adults treated during childhood between 1945 and 1974, having lived in more than 5 years from treatment till the age of 21, and compared with 479 members of their siblings, those treated for medulloblastoma had significantly more health problems, more physical and/or intellectual incapacity to work and drive (44). In addition, adults who had been treated for a brain tumor in childhood (especially a MB) had a greater risk of suicidal thoughts (7).

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Conclusion

Medulloblastoma is a malignant tumor of the cerebellum with high metastatic potential. The standard treatment of nonmetastatic medulloblastoma after total or subtotal resection in children over five years includes irradiation of the central nervous system. For standard as well as high risk forms (metastases in the central nervous system and/or incomplete resection) and cases affecting children under five years, the main recommendation is the treatment of these patients as revealed in multicenter trials done in specialized settings by neurosurgical, pediatric oncology and radiation therapy teams conversant with this pathology. It is from these multidisciplinary teams that the role of chemotherapy in high-risk forms and postoperative treatment with chemotherapy alone in children under five are explored.

After treatment, a multidisciplinary monitoring for development of neurocognitive function, spinal growth, hypothalamic-pituitary function as well as hearing and kidney function is essential to allow for early management of the sequelae of the disease and treatment.

Promising advances are based on molecular biology, which in association with the clinical context and histology do not only help to define the risk groups, but also to detect new targets accessible to targeted molecular therapies currently under trial.

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