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Neuropsychological consequences of childhood medulloblastoma and possible interventions: A review.

Revue sur les conséquences neuropsychologiques d'un médulloblastome pendant l'enfance et les interventions possibles

Neuropsychological consequences of childhood medulloblastoma

Doger de Spéville, Elodie (1,2,3), Kieffer, Virginie (3,4), Dufour, Christelle (3), Grill, Jacques (3),
Noulhiane, Marion (1,2), Hertz- Pannier, Lucie (1,2), Chevignard, Mathilde*(5,6,7)

*Auteur correspondant :

Dr Mathilde Chevignard
Service de Rééducation des Pathologies Neurologiques de l'Enfant
Pôle de Rééducation et Réadaptation de l'Enfant
Hôpitaux de Saint Maurice
14, rue du Val d'Osne
94410 Saint Maurice
Tel: 01 43 96 63 40
Fax: 01 43 96 65 47
m.chevignard@hopitaux-st-maurice.fr

1- INSERM U1129, CEA, Paris Descartes University, Paris, France

2- UNIACT, Institut Joliot, DRF, Neurospin, CEA, Paris Saclay University, Gif-sur-Yvette, France

3- Department of Pediatric and Adolescent Oncology, Gustave Roussy, Villejuif, France

4- CSI Department for Children with Acquired Brain Injury, Hopitaux de Saint Maurice, Saint-Maurice, France

5-Rehabilitation Department for children with acquired neurological injury, and Outreach team for children and adolescents with acquired brain injury, Saint Maurice Hospitals, 14, rue du Val d'Osne. 94410 Saint Maurice, France

6- Sorbonne Universités, UPMC Univ Paris 06, UMR 7371, UMR_S 1146, LIB, F-75005, Paris, France.

7-GRC n°18, Handicap Cognitif et Réadaptation (HanCRE); UPMC Paris 6; Paris; France.

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Abstract:

Background: Children who have been treated for a medulloblastoma often suffer long term cognitive impairments that often negatively affect their academic performance and quality of life. In this article we will review the neuropsychological consequences of childhood medulloblastoma and discuss the risk factors known to influence the presence and severity of these cognitive impairments and possible interventions to improve their quality of life.

Methods: This narrative review was based on electronic searches of PubMed to identify all relevant studies.

Results: Although many types of cognitive impairments often emerge during a child's subsequent development, the core cognitive domains that are most often affected in children treated for a medulloblastoma are processing speed, attention and working memory. The emergence and magnitude of these deficits varies greatly among patients. They are influenced by demographic (age at diagnosis, parental education), medical and treatment-related factors (peri-operative complications, including posterior fossa syndrome, radiation therapy dose, etc.), and the quality of interventions such as school adaptations provided to the child or rehabilitation programs that focus on cognitive skills, behavior and psychosocial functioning.

Conclusion: These patients require specialized and coordinated multidisciplinary rehabilitation follow-up that provides timely and adapted assessments and culminates in personalized intervention goals being set with the patient and the family. Follow-up should be continued until referral to adult services.

Key words: childhood; medulloblastoma; cognitive impairments; risk factors; interventions

Résumé :

Introduction : Les enfants qui ont été traités pour un médulloblastome souffrent souvent de troubles cognitifs qui impactent leur autonomie, leur réussite scolaire et leur qualité de vie. Cet article a pour objectif de passer en revue les domaines cognitifs qui sont souvent affectés chez les enfants traités pour un médulloblastome et les facteurs de risque pouvant influencer leur présence et leur sévérité, ainsi que les interventions possibles permettant d'améliorer la qualité de vie de ces patients.

Méthodologie : La bibliographie de cette revue a été réalisée avec l'interface d'accès PubMed afin d'identifier les études et revues les plus pertinents.

Résultats : Bien qu'une variété de difficultés cognitives soit rapportée chez les enfants traités pour un médulloblastome, les domaines cognitifs les plus souvent touchés sont la vitesse de traitement, l'attention et la mémoire de travail. L'émergence et la sévérité de ces déficits sont très variables chez les patients, et sont influencées par de nombreux facteurs tels que des facteurs démographiques (âge au diagnostic, éducation parentale), les facteurs liés au traitement (complications périopératoires, y compris le syndrome de la fosse postérieure, la dose de radiothérapie, etc.), mais également la qualité des interventions telles que les adaptations scolaires ou les programmes de réadaptation axés sur les habiletés cognitives, le comportement et le fonctionnement psychosocial de l'enfant.

Conclusion : Ces patients ont besoin d'une prise en charge multidisciplinaire spécialisée et coordonnée, offrant des évaluations adaptées, menant à des objectifs d'intervention personnalisés décidés avec le patient et la famille. La prise en charge doit être poursuivie jusqu'à l'orientation vers les services pour adultes.

Mots clés : pédiatrie ; médulloblastome ; troubles cognitifs ; facteurs de risque ; interventions

Medulloblastoma is one of the most common malignant childhood brain tumors, arising in the posterior fossa. As a result of improved treatment, event-free survival has significantly increased, but this long-term survival has brought to light the resulting neurocognitive deficits. Consequently, research in this domain has taken a prominent role in pediatric oncology. In this paper, we will review the neuropsychological consequences of childhood medulloblastoma, discuss the risk factors known to influence the presence and severity of these cognitive impairments and describe interventions that have been developed to improve the patients' quality of life.

The literature search was performed using the PubMed database with combinations of the following keywords: "pediatric oncology"; "medulloblastoma"; "posterior fossa tumor"; "neuropsychological impairments"; "cognitive impairments"; "core deficits"; "risk factors"; "radiation therapy"; "chemotherapy"; "surgery"; "posterior fossa syndrome"; "rehabilitation program". Inclusion criteria were articles published in a peer-reviewed journal and written in French or English. Articles were screened by the relevance of their abstract. The selected ones were read carefully in their entirety.

I. Cognitive impairments

To our knowledge, the first study in this field dates back to 1969, when Bloom *et al.* (1) noted the elevated rate of “cognitive dementia” in this population.

Since then, studies in this domain have proliferated and show that children treated for a medulloblastoma (2–4) had a progressive the decrease in their intelligence quotient (IQ) over time (2-4 points/year) (5–7). This decline was not due to a loss of previously acquired knowledge, but rather to a reduced rate of subsequent new learning, compared to healthy same-age peers (8). Those deficits in turn impact the patients’ academic performance (e.g. acquisition of reading and mathematical skills) (7,9,10) and more generally, their quality of life (11,12). Several authors believe the overall intellectual decline reported in the literature is due to alterations of more specific cognitive core components (13), such as processing speed, attention and working memory (2,3)

Processing speed is characterized by how quick a person can take in, process and respond to information. This information can be visual, like symbols (e.g. letters, numbers) or auditory (e.g. words). An early decrease of information processing speed has frequently been reported in these patients. It is thought to be the first difficulty to arise after treatment and seems to be specifically correlated with the craniospinal irradiation (CSI) dose (14–17).

Attention difficulties are also frequently observed in these children (18–21). They probably appear later than processing speed decline (16), and include mainly selective and sustained attention difficulties (18,21). These children have difficulty focusing on a task/stimulus, while ignoring distractor stimuli, and maintaining their vigilance. Interestingly, these attention deficits are associated directly with demyelination caused by CSI (16,19). According to one study, 10 years after

treatment that includes CSI, the prevalence of attention difficulties in children with posterior fossa tumor (PFT) could be as high as 78% for sustained attention and 90% for motor attention tasks (22).

Working memory is a memory system allowing temporary maintenance of a limited amount of information and its manipulation. Several studies have explored the development of this function, which is crucial to the success of many academic tasks (arithmetic, reading, listening and taking notes) in children with PFT (23). King *et al.* (24) compared the neuropsychological performance of a group of children treated for cerebellar tumors versus children with third ventricular tumors. Unlike the group of children with third ventricle tumors, the group with cerebellar tumors had specific deficits in working memory and attention. A working memory deficit might emerge very early with a continued decline over time. A decline in the working memory index of children treated for brain tumors (12/18 were treated for a medulloblastoma) was observed very early after the start of their neuropsychological follow-up (16). More interestingly, Edelstein *et al.* 2011 showed that—despite stable IQ scores 20–40 years after diagnosis—working memory was the only index that continued to decline over the long term.

Other types of cognitive impairments also often emerge during these children's subsequent development in a number of neuropsychological areas, such as executive functions, fluency, problem solving, planning (25,26), episodic memory (22,27–29) or control and identification of emotions (30). Some of these difficulties emerge very early after disease onset, while others emerge much later (several years), as deficits become evident when environmental demands increase, and cognitive functions fail to develop at the expected rate. The emergence and magnitude of these deficits is highly variable within patients. Factors influencing the outcome have been summarized in a recent literature review (13). They include

demographic factors (age at diagnosis, parental education and socio-economic status, used as proxies for the environment in which the child lives), medical and treatment-related factors (peri-operative complications, including posterior fossa syndrome, radiation therapy dose, etc.), and interventions and school adaptations provided to the child.

II. Risk factors known to influence the presence and severity of cognitive impairments

In the literature, several factors have been identified as predictive of the risk of late cognitive impairments. The first is related to the disease—the tumor location and the age at diagnosis. The second factor is related to the treatment used—surgery, peri-operative complications, chemotherapy and radiation therapy. The third factor is the environment the child grows up in, and particularly the family's influence.

A. Disease-related risk factors

1) Tumor location

The anatomical location of these tumors—inside and/or adjacent to the cerebellum—puts the cerebellar pathways and cerebellar functions at risk during the surgical procedure (4). The cerebellum is composed of three parts: the vermis and two cerebellar hemispheres (one on each side). It plays an important role in sensory-motor functions, balance control and vestibulo-ocular reflex (31), but also in a wide range of cognitive functions, including language, processing speed, memory and executive functions (32–35). Laterally located in the hemisphere, the serrated nuclei, which are the most voluminous deep nuclei, have been described as central relays in the anatomical pathways connecting the cerebellum with the non-motor cerebral

cortex (36).

Today, it is an accepted fact that a lesion in the cerebellum causes neurocognitive deficits. However, the relationship between the lesion's location, type and severity of deficits remains unclear. Vermis injuries are associated with a higher risk of cognitive and affective impairments (37–40). The type of deficits and lesion lateralization were also correlated in children treated for medulloblastoma. A tumor in the right cerebellar hemisphere is associated mainly with linguistic and logical reasoning deficits, whereas a left hemisphere lesion induces attentional and visual spatial deficits (37,41). In children with PFT, lesions to the dentate nuclei on postoperative imaging were associated with lower IQ and more severe motor dexterity difficulties (40).

2) *Age at diagnosis*

Young age at diagnosis of medulloblastoma is a risk factor for long-term cognitive impairments (7,8,42,43). In a longitudinal study (3 years post-diagnosis), Ris *et al.* (5) showed that children treated before the age of 7 had greater cognitive decline than in those treated at a later age. This effect is mainly due to CSI (42). Younger patients treated with CSI with or without chemotherapy have more deficient myelination and a greater loss of white matter over time, leading to greater cognitive deficits. However, no association between age at diagnosis and cognitive impairments has been found in several studies (17,44,45). In other studies, an effect of age at diagnosis was found only for certain cognitive measures (42,46), suggesting that the occurrence of impairments is multifactorial. For example, in the study by George *et al.* (46), the average verbal, performance and full-scale IQ were significantly higher in children with PFT diagnosed at 6 years or later than in younger children. On the other hand, their average performance on memory assessments (WRAML) was similar. Palmer

et al. (6) provided an alternative explanation for these discrepancies. Age at diagnosis influences the speed of cognitive decline more than its intensity. In the youngest children, cognitive decline begins on average 2 years after diagnosis and then stabilizes. On the other hand, the greatest cognitive difficulties begin to emerge later after the diagnosis. According to Palmer *et al.* (6), the decrease in IQ over time between younger and older patients is comparable 6 or 7 years post-diagnosis. Future studies should use multivariate analyses to take into account not only age at diagnosis, but also other treatment-related factors (peri-operative complications and radiation therapy dose), as well as environmental factors such as socio-economic status, which are strong moderators of a number of outcomes in children treated for medulloblastoma (13).

B. Tumor and treatment-related factors

1) Post-operative cerebellar mutism

Cerebellar mutism syndrome is a postoperative clinical entity characterized by diminished or absent discourse during a period of time, ataxia, hypotonia and emotional lability (47–49). The incidence of cerebellar mutism syndrome varies across studies (8-25%) (50,51). Left-handedness, and disruption of the connection between the right cerebellum and left frontal cortex have been associated with the occurrence of cerebellar mutism syndrome. Brain stem infiltration and tumor histology (i.e. medulloblastoma) also appear to be frequently associated with the development of cerebellar mutism syndrome (52,53). Pre-existing language impairment seems to increase the probability of cerebellar mutism (53). On the other hand, the hypothesis that the surgical techniques used to reach the fourth ventricle (incision of the vermis vs. telovelar approach) could increase its occurrence has not been confirmed (54). The neuropsychological impairments following cerebellar

mutism syndrome resulting from posterior fossa tumor surgery are now well known (47,50). Despite the disappearance of cerebellar mutism after a few days to one month, it remains associated with a high risk of immediate and long-term cognitive impairment (53,52).

Symptoms beyond those described in cerebellar mutism syndrome have also been reported in these children and are more widely known as the so-called posterior fossa syndrome (49,56). In addition to cerebellar mutism, it is characterized by behavioral disturbances (personality change, apathy, memory or attention problems), language difficulties (agrammatism, word finding difficulties, dysarthria) and motor difficulties (initiation of movement, cranial nerves palsies) (47,49,57). Interestingly, this combination of symptoms—already described in adults (58)—is known as the “cerebellar cognitive affective syndrome”.

2) *Hydrocephalus*

The specific effect of hydrocephalus on the functional and academic achievement of children with medulloblastoma, or more generally with PFT, remains less clear. Controlling for the potential effect of clinical and demographic variables (age at diagnosis, radiation therapy, socioeconomic level), Hardy *et al.* (59) showed that children with medulloblastoma treated for hydrocephalus had significantly lower IQ and performance in mathematics, writing and visual-motors tasks than those who did not require hydrocephalus treatment. While several other studies have corroborated these findings and extended them to other cognitive domains (memory, academic and social performance, dysarthria and ability to cope with daily tasks, etc.) (45,60–62), others found no effect of hydrocephalus on cognitive performance (63,64), with sometimes contradictory results (65). Finally, other peri-operative or hydrocephalus treatment-related complications, such as meningitis or shunt infection have also been

associated with a negative impact on intellectual ability (64).

3) *Radiation therapy*

Radiation therapy is now considered to be one of the major factors leading to neurocognitive deficits (43,44,66–68). More specifically, craniospinal radiation therapy (7,14,44,69), the volume receiving the dose escalation—conventionally referred to as “boost” (70)—and the fractionation (67,71) appear to be particularly related to the progressive intellectual deterioration reported in children treated for a brain tumor.

Impact of craniospinal irradiation on cognitive development

Grill *et al.* (44) reported a clear association between craniospinal dose and Wechsler-scale performance (72), particularly for full-scale and verbal IQ in 31 patients treated for ependymoma or medulloblastoma. This effect has been replicated many times in children treated for PFT and has also been extended to other cognitive functions such as attention, executive functions, visuo-motor coordination, emotions or academic skills (reading, mathematics) (7,14,73,74). Reducing the dose to the craniospinal axis (25 Gy or 18 Gy)—especially for younger children and standard-risk medulloblastoma—appears to help preserve cognitive functions. However, a substantial decrease in performance on Wechsler's scales seems to persist over the long term (5).

Impact of the boost on cognitive development

Another attempt to better preserve cognitive performance of children with medulloblastoma has been to reduce the volume receiving the boost (i.e., posterior fossa). Even if the dose reduction on the craniospinal axis decreases the doses

delivered to the brain as a whole, the boost on the entire posterior fossa produces higher doses in adjacent regions such as the temporal lobes, hippocampus, brainstem or hypothalamus (20,70). Reducing the volume of the posterior fossa boost to the tumor bed could significantly decrease the volume of healthy tissue receiving the highest dose. Recently, Moxon-Emre *et al.* (75) confirmed this hypothesis by showing that children treated for medulloblastoma whose craniospinal radiation dose and dose escalation volume had been reduced maintained a stable IQ over time. In contrast, those who had only the dose reduced on the craniospinal axis or the volume receiving dose escalation had a performance decrease over time.

Regional effect of radiation therapy on cognitive functions

Several recent studies have focused on the specific effect of irradiation in certain brain regions on the cognitive performance of children treated for a medulloblastoma (7,70,76). Armstrong *et al.* (76) used a self-administered questionnaire to study the relationships between the maximum doses received in different brain regions (temporal, frontal, parieto-occipital) and cognitive complaints in the last 6 months in patients treated for a childhood brain tumor. In patients treated for a medulloblastoma, they found a strong association between the maximum dose received in the temporal lobes and the presence of attention, information-processing (task efficiency) and planning (organizational) difficulties. In a similar way, Doger de Speville *et al.* (77) found an association between processing speed decline and the high dose delivered to the temporal lobes and posterior fossa. In contrast, working memory decline seemed to be related more to the dose delivered to the orbitofrontal regions.

With regards to overall intellectual functioning, Merchant, *et al.*, (7) analyzed the impact of the mean doses in several regions (i.e. whole brain, temporal lobe,

hippocampus and posterior fossa) on IQ change over time in children treated for a medulloblastoma. They concluded that among the areas evaluated, the posterior fossa appeared to be the most tolerant to radiation therapy, followed by the temporal lobes, the hippocampus and finally the supratentorial region (i.e. the brain). However, the inverse pattern was observed in children treated for an ependymoma (78). In fact, there was an association between the mean dose delivered to the posterior fossa and the IQ decrease over time, whereas this association was not found for the supratentorial region. According to the authors, this lack of association is not related to a lower average dose being delivered (≈ 14 Gy) to the brain compared to the posterior fossa. The deleterious effects on IQ of whole brain irradiation have already been observed in patients with similar doses (69) or much lower doses (79,80). The authors attributed these differences to the methodology: the use of a dose index (i.e. average dose in the region) versus the percentage of volume receiving dose range (i.e. 0–5 Gy).

4) Chemotherapy

Chemotherapy has also been implicated in the emergence of cognitive difficulties in children treated for a medulloblastoma or more generally for a brain tumor (45,81). However, its specific contribution remains highly debated. In a study looking at 52 children treated for malignant and benign brain tumors, those who received chemotherapy had lower IQs than who did not (45). However, the authors of this study did not appear to take into account important factors such as benign/malignant tumors vs. presence/absence of radiation therapy. Chemotherapy has also been associated with immediate and long-term memory impairment in patients with childhood brain tumors (82). According to the authors, chemotherapy could be a risk factor for future academic difficulties. However, other studies have shown no

significant adverse effects of chemotherapy on cognitive development when compared to radiation therapy (6,73,83,84).

One reason for these disparities is probably the fact that certain types of chemotherapy have unequal long-term consequences, some of which are more toxic, such as methotrexate. The administration of methotrexate significantly increases the occurrence of cognitive difficulties in children, compared to other drugs (81). The authors showed that groups treated with radiation therapy and chemotherapy including methotrexate had significantly lower cognitive performance than controls, especially in younger patients. In contrast, those treated with radiation therapy and chemotherapy without methotrexate had similar results to controls in most cognitive tests. Methotrexate is associated with white matter neurotoxicity and may cause leukoencephalopathy (85). It is currently difficult to estimate the impact of chemotherapy on cognition in patients treated for a brain tumor due to many confounding factors. In children treated for a medulloblastoma, chemotherapy is most often associated with radiation therapy, and this combination may result in more diffuse white matter injury (86,87).

C. Environmental factors

In addition to factors related to the disease and its treatment, the patient's family and school environment influence subsequent cognitive development. A recent study showed that the family's socioeconomic level, measured by the mother's occupation, was a significant predictor of the level of neurocognitive deficits in children treated for medulloblastoma (88). Similarly, Palmer *et al.* (6) analyzed the effect of socio-economic status (measured by the parents' education level) on IQ change over time in children treated for medulloblastoma. Interestingly, a significant difference in average IQ was observed between high- and low socio-economic level groups and

this difference was maintained as scores decreased over time. In other words, IQ differences exist between children of different socio-economic levels, but the IQ decline over time seems to be similar across groups.

Socioeconomic level and family functioning were also reported to be associated with social adjustment or quality of life (13,89,90). Indeed, a stressful family environment and the inability of parents to develop strategies to adapt to the constraints associated with the disease ("coping resources") are factors associated with a higher risk of impairment (91).

Finally, school adaptations and appropriate and timely rehabilitation interventions may have a significant impact on the academic performance of patients with PFT, promoting the implementation of strategies to minimize the impact of their cognitive difficulties (28,92,93). These environmental factors—which have a major influence on outcomes in other acquired brain pathologies such as traumatic brain injury—remain underexplored in children treated for medulloblastoma (13). Nonetheless, these variables could have a significant impact on the intellectual development of these children, and probably more generally children with brain tumors. Accounting for them would probably explain a non-negligible part of the variability observed among children treated for medulloblastoma.

III. Interventions aimed to improve cognitive functioning, behavior and psychosocial functioning, academic achievement and community integration

Given the broad range of deficits reported in many domains in this population, early comprehensive assessment is necessary. Given the delayed expression of cognitive deficits—impacting school, everyday life and long-term community integration—assessments should be repeated over time, either at key transition periods (e.g.

before entering primary or secondary school, or when vocational training questions arise), or when difficulties arise. Assessments should take into account various demographic, tumor- and treatment-related factors, as well as the environment in which the child lives, i.e. his/her family environment. The resources available at school and in the community are also very important to consider. Those assessments should allow early and individualized intervention and rehabilitation programs to be implemented as necessary. Careful assessment and discussion with the family should allow an adequate level of care to be implemented, while minimizing care-related burden. Thus it is important to provide systematic long-term coordinated multidisciplinary follow-up until the child transitions to adult services. Individualized child- and family-based care can be implemented as needed (94,95). These individualized interventions should ideally be holistic and reviewed and adjusted regularly, as needs evolve over time. Interventions can thus include specific motor or cognitive interventions designed to improve a given skill, or a combination of interventions focused on various deficits. Psychosocial and school interventions, or implementation of special education services are also often needed at various times post-diagnosis, as well as family support interventions. For example, this can include interventions by physiotherapists, occupational therapists, speech and language therapists, psychologists and neuropsychologists, social workers, special school teachers, etc. (94,96).

As an example, a comprehensive rehabilitation program devoted specifically to children and adolescents with acquired brain injury (including brain tumors) has been developed in the Paris area by the Saint-Maurice Hospitals. This program provides multi-disciplinary rehabilitation—which can start in the hospital if needed (in the most severe cases)—early and repeated contact with the professionals in the community who will support the child over the long term, as well as family support programs,

addressing educational issues, and discharge planning neuropsychological assessments, which reveal the need for interventions and school adaptations when necessary (94).

Also, a multidisciplinary consultation meeting was created in 1997 at the Gustave Roussy cancer center, in collaboration with family associations and the Saint-Maurice Hospitals (97), in which complex cases (but not complex enough to require the prolonged involvement of the outreach team) are examined in detail. Several professionals from the pediatric oncology department attend the meeting (oncologist, neuropsychologist, psychologist, child psychiatrist, educator, and specialized teachers who provide in-hospital schooling, etc.). Professionals caring for the child in the community, such as speech and language therapists, occupational therapists or physiotherapists are invited as well. Finally, an educator and a social worker from the Saint Maurice outreach team also attend the meeting for teenagers. During this meeting, the team proposes an intervention plan, including rehabilitation and school adaptations (modified curriculum, implementation of a personal school assistant, special education services, etc.). Those suggestions are made to the family. If they agree, the necessary work will be done to implement those decisions and a written document detailing the school adaptations is sent to the family, the teacher and the therapists working with the child.

Rehabilitation should typically be combined with simple environmental interventions, such as appropriate placement in the classroom; adaptations of school curriculum and testing formats; providing more time to perform assignments; giving shorter assignments or using different testing formats to reduce the memory retrieval load (e.g. multiple choice or true/false responses); having the instructions clarified if needed; using written handouts to reduce the need to copy text from the blackboard;

reducing the amount of homework, and promoting the use of computers to improve writing efficiency when needed (92,94). All of these multidisciplinary holistic programs usually yield good results (94,95). Unfortunately, one of the most frequent limitations of these holistic interventions is that they rarely measure treatment effects using ecological tasks that would show improvement of the patients' performance in everyday life—they usually measure performance on various tests pre- and post-intervention. Also, they hardly ever measure generalization of treatment effects to untrained tasks and the transfer to other contexts, as well as long-term maintenance of treatment effects after treatment completion (for a review on those issues, see Krasny-Pacini *et al.* (98,99)).

Various approaches have been developed and are detailed below.

A. Use of medications

There have been a few studies on the use of stimulants to improve neurocognitive and learning outcomes in children diagnosed with brain tumors. They have been summarized in a recent systematic review (100) that identified a total of 226 participants with ALL or brain tumors (n=121) who received cranial radiation therapy, randomized across four clinical trials. Promising results were found for methylphenidate in improving attention, processing speed, cognitive flexibility, social skills and academic competence, using direct and indirect parent- and teacher-rating measures. In the long-term follow-up of treatment effectiveness, parent and teacher ratings of attention, social skills and behavior were significantly improved, however changes on standardized measures of academic attainment did not reach statistical significance. Results also suggest that male gender, older age when treated and

higher baseline IQ are predictive of greater response to methylphenidate at a dose of 0.6 mg/kg.

Lithium is an agent that has been used for psychiatric disorders for decades, but recently there has been emerging evidence that it can have a neuroprotective effect. Lithium exerts neuroprotective effects and is associated with less cognitive loss in various brain-injury models, including after CSI (101,102). One study used three-dimensional magnetic resonance imaging and brain segmentation to evaluate the effect of lithium on grey-matter volume in patients with bipolar mood disorder. Four weeks of lithium treatment increased brain grey-matter content (103) and hippocampal volume (104). There has been one early-phase study in adults in which lithium was used as a neuroprotectant (105,106). A phase I study in children with brain tumors will be performed in Europe.

B. Interventions aimed at improving a specific cognitive skill

Cognitive rehabilitation aims to restore lost cognitive functions, or at least to teach the patient the skills needed to compensate for cognitive deficits that cannot be restored.

As an example, Slomine and Locasio (107) reviewed cognitive rehabilitation programs for children with acquired brain injury (ABI) and Wolfe *et al.* (23) reviewed interventions focused on executive dysfunction in posterior fossa tumor survivors. Overall, there are very few experimental rehabilitation studies that have included brain tumor survivors, but there is emerging evidence of cognitive rehabilitation being effective. Positive effects are often found for cognitive functions that have been

specifically trained. However, long-term maintenance of the effects, generalizability to other untrained tasks and transfer to everyday life activities are very rarely reported.

Butler and Copeland (108) developed a promising program aimed at improving attention deficits in cancer survivors that combined various approaches: attention process training, metacognitive strategies, and cognitive behavioral strategies. The program consisted of 20 two-hour sessions over 4 to 5 months with a therapist. Results of a pilot study were encouraging, but there was no evidence of generalization and transfer (108). Results of a larger controlled study (109) (waitlist control group) with 161 childhood cancer survivors who had undergone CNS treatment, revealed improvements in brief attention, working memory, memory and learning strategies, vigilance, as well as parents' perceptions of cognitive problems and attention, and in all academic domains except reading comprehension.

Hardy *et al.* (110) tested a computerized home-based 12-week intervention program in a small group of cancer survivors, and reported a trend towards better working memory scores, along with a decrease in parent-reported attention problems.

Kesler *et al.* (111) performed a pilot study of an online cognitive rehabilitation program (8 weeks – 40 sessions), focused on cognitive flexibility, attention and working memory in childhood cancer survivors. They concurrently studied brain activation in functional MRI. Post-intervention, improvements were found in processing speed, cognitive flexibility, verbal and visual declarative memory scores, as well as significantly increased pre-frontal cortex activation compared to baseline. Such studies are promising, but as most published studies, no long-term outcomes or mention of generalization to untrained tasks and transfer to everyday life activities was made. These issues should be priorities for future studies (112).

Finally, since recent data indicate that aerobic exercise has been associated with improved cognitive outcomes in children and in aging adults (113–115), a pilot study

performed by Wolfe *et al.* (116) used a functional MRI protocol to investigate the relationship between working memory and cardiorespiratory fitness in 9 adolescent survivors of posterior fossa tumors treated with CSI. Higher cardiorespiratory fitness was related to better performance on a behavioral measure of working memory and more efficient neural functioning in the functional MRI task. Results suggested that cardiorespiratory fitness might be associated with more efficient neural processing in survivors. Future studies should explore the direct effects of cardiovascular exercise on cognitive functioning in this population. This possibility is supported by the review by Diamond and Lee (117) on interventions shown to aid executive function development in children 4 to 12 years of age. They found that aerobic exercise robustly improves prefrontal cortex functions and executive functions (EF) in adults. These findings are supported by studies performed in children also: running / aerobic exercise improves 8 to 12 year-olds' cognitive flexibility and creativity, and significantly more than standard physical education; it improves EF and math in 7 to 11 year-old overweight children. Diamond and Lee (117) suggest that sports might benefit EFs even more than aerobic exercise alone, as sports also require sustained attention, working memory, and disciplined action, and they bring joy, pride, and social bonding. Recently, in a clinical trial with crossover of exercise training versus no training, Riggs *et al.*, (118) showed that exercise training promoted the increase of white matter and hippocampal volume, and improved reaction time in children treated with CSI for brain tumors.

C. Interventions focused on behavior and social skills

Interventions for school re-entry are necessary, but not sufficient. Information needs to be given to teachers and peers, as well as information on the child's strengths and weaknesses and ways to help him/her most effectively. Social skills training is also

recommended to optimize social reintegration, improve peer relationships and prevent long-term social isolation, which are important to the child's subsequent development (3).

Slifer and Amari (119) reviewed the behavioral interventions available for children with ABI. Most of the research in this field is based on case studies, or studies employing single-subject experimental designs. Overall, the literature supports the efficacy of such behavioral interventions in childhood ABI, across ages, injury severities, and stages of recovery. The authors provide guidelines for behavior management that can be very useful in clinical practice.

Social skills appear to be important determinants of social reintegration. Recurrent themes emerging from group discussions with brain tumor survivors are 'being made fun of by peers' and 'lack of friendships with classmates' (120). As these difficulties do not seem to improve spontaneously over time, and tend to persist into adolescence and adulthood, Barrera and Schulte (120) developed a social skills intervention program. It targets children aged 8–16 years, is performed in a small group format, and aims to improve the following social skills: assertiveness, handling teasing by peers, making new friends, cooperation, empathy and conflict resolution. The intervention consisted of eight two-hour weekly sessions, focusing on the following social skills: social initiation and friendships, cooperation, managing teasing and bullying, conflict resolution, empathy, and assertion with self-confidence building. Overall, the intervention was feasible, and participants and their parents reported that it helped them improve relationships with friends and peers or parents/family, and helped them express feelings about experiences with peers and parents/family. Most participants said that meeting other children with similar experiences was beneficial. The intervention led to significant improvement in parent-rated social skills, self-control and health-related quality of life, without changes in behavior or depression

(which was not present to start with). Improvements were maintained at the 6-month follow-up.

D. Interventions focused on families

Disability and the disease affect not only the child, but the whole family. In addition to the cancer-related issues, changes in the child's personality, behavior and emotions could be conceptualized as the child's response to the poor fit between the environmental expectations held of him and his current neurodevelopmental capabilities. As the growing child encounters increasing demands and fails to make age-appropriate acquisitions, the person–environment fit can worsen, thus contributing to an expanding pattern of disability as time goes by. Cole *et al.* (121) reviewed studies in which family interventions for pediatric ABI were assessed, and then provided theoretical clinical guidelines for those interventions to guide clinicians. Unfortunately, few studies were included in this review, and even fewer were controlled studies. They were classified as “promising but not yet validated” or “probably effective”. Since then, a number of online programs have been developed and assessed using robust randomized controlled studies, and it has been shown that age-adapted family problem solving interventions are effective, mostly in traumatic brain injury context (122,123). Those studies may be relevant for children and youth with brain tumors as well.

Ideally, the various interventions should be tailored to each child's deficits, strengths and weaknesses, to the availability of care in the community, and to the child's and family's choices and preferences. The interventions should be coordinated by an experienced rehabilitation team working closely with the education team.

IV. Transition into adulthood

Long-term survivors of childhood medulloblastoma often suffer long-standing motor and cognitive deficits (22,27), which impact their independence in adulthood and employment. Despite often being able to obtain a diploma, patients can have difficulty finding and especially maintaining a job, or they might need special adaptations in their workplace (i.e. reducing the pace, avoiding multi-tasking, etc.) or need to work less (i.e. working part-time) because of disabling persistent fatigue. Further, some patients may lack motivation or energy, or suffer mood disorders such as anxiety and depression.

Recently, there has been growing interest in the transition to adulthood for survivors of childhood brain tumors (124–126). In France, a long-term oncology follow-up clinic was created in January 2012 at two cancer centers (Gustave Roussy and Institut Curie) (127). All survivors over 18 years of age with at least 5 years' follow-up since diagnosis were invited to attend this clinic. The outreach team for children and youth with ABI in the Saint Maurice Hospitals also has developed a specific support system for the older teenagers and young adults (16–25 project). This team aims to help young adults find adequate professional training, develop independence (e.g. in administrative documents), and refine a plan defining which adult structure would be most adequate for their subsequent follow-up (94). The patients who need physical medicine and rehabilitation follow-up in an adult department are referred to the appropriate unit based on their needs. Some families are also referred to an association composed of lawyers that provide legal guidance and assistance to young people about administrative and financial issues. They also provide skill assessments and help patients find a career path that takes into account their cognitive impairment.

Conclusion

Medulloblastoma is a chronic disease. Patients in remission often suffer a number of very diverse, long-standing impairments (endocrine, growth and neurological deficits, neuropsychological impairments, mood, emotional and psychosocial difficulties, etc.), which have negative consequences on their social participation and professional integration. In addition to oncological and endocrine follow-up, they require specialized and coordinated multidisciplinary rehabilitation follow-up that provides timely and adapted assessments. The assessments should identify the patient's strengths and weaknesses, as well as the patient's and family's goals. Taken together, these elements help to define and implement personalized intervention goals with the patient and their family. The goals should be reviewed over time as impairments appear or change with increasing demands (especially at school). Follow-up should be continued until the child is old enough to be referred to adult services.

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