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Core deficits and quality of survival after childhood medulloblastoma: a review

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Abstract

Background. Medulloblastoma is the most common malignant central nervous system tumor in children. Treatment most often includes surgical resection, craniospinal irradiation, and adjuvant chemotherapy. Although survival has improved dramatically, the tumor and its treatments have devastating long-term side effects that negatively impact quality of survival (QoS). The objective was to review the literature on QoS following childhood medulloblastoma.

Methods. This narrative review is based on a Medline database search and examination of the reference lists of papers selected.

Results. Frequent problems after medulloblastoma treatment include medical complications, such as long-term neurological and sensory (hearing loss) impairments; endocrine deficits, including growth problems; and secondary tumors. Neurocognitive impairment is repeatedly reported, with decreasing cognitive performances over time. Although all cognitive domains may be affected, low processing speed, attention difficulties, and working memory difficulties are described as the core cognitive deficits resulting from both cerebellar damage and the negative effect of radiation on white matter development. Long-term psychosocial limitations include low academic achievement, unemployment, and poor community integration with social isolation. Important negative prognostic factors include young age at diagnosis, conventional craniospinal radiotherapy, presence of postoperative cerebellar mutism, and perioperative complications. The influence of environmental factors, such as family background and interventions, remains understudied.

Conclusion. Future studies should focus on the respective impact of radiation, cerebellar damage, genomic and molecular subgroup parameters, and environmental factors on cognitive and psychosocial outcomes. Long-term (probably lifelong) follow-up into adulthood is required in order to monitor development and implement timely, suitable, multi-disciplinary rehabilitation interventions and special education or support when necessary.

Key words

medulloblastoma | neurocognitive deficit | psychosocial outcome | quality of survival | quality of life

There is a growing number of childhood cancer survivors[1] and it is becoming increasingly important to improve our knowledge of the long-term adverse effects of disease and treatments in order to provide appropriate health care and decrease the risk of adverse psychosocial effects.[2] It has been estimated that 62.3% of pediatric cancer survivors have at least one chronic or late-occurring condition, with 27.5% presenting a severe or life-threatening condition.[3,4] However, self-reported or proxy-reported quality of life among adolescent and adult survivors of childhood cancers is often little-related to the degree of disability and may overall be good.[5]

Among these survivors, children treated for central nervous system (CNS) malignancies in particular are at high risk for neurocognitive impairment, medical complications, and poor social outcome.[6,7] For instance, lower-than-expected educational attainment and increased utilization of special education services have been repeatedly reported in cases of CNS neoplasm and/or cranial radiation therapy.[8–12]

Incidence of CNS Tumors and Medulloblastoma

The overall age-standardized incidence rate of childhood CNS tumors in Europe has been reported to be 29.9 per million, the most frequent types being astrocytoma and medulloblastoma.[13] Medulloblastoma, the most common malignant brain tumor in children, is an embryonic tumor of the cerebellum or fourth ventricle accounting for 12% to 20% of childhood CNS tumors, with median age of diagnosis 5 to 7 years and a slight male preponderance.[14] Medulloblastoma is rare in the adult population,[15] although it accounts for a meaningful percentage of all cases over the age of 18 years.

Pathophysiology of Medulloblastoma

The main pathological categories of medulloblastoma are: classic, nodular desmoplastic, or large cell/anaplastic. Four molecular subgroups have been described (WNT pathway activation, SHH pathway activation, group 3, and group 4) and other molecular criteria are also used (MYC and MYC-N amplification, P53 mutation).[16–18]

Low-risk medulloblastoma in older children (above 3 to 5 years) is defined by localized, completely or near-completely resected tumors, classic histology, and WNT pathway activation. *Standard risk* medulloblastoma in the same age group has the same staging characteristics, but does not show the low-risk WNT pathway activation or the high-risk biopathological risk factors (such as large cell/anaplastic histology, MYC amplification, MYC-N amplification, or P53 mutation, the last two criteria often being combined with SHH pathway activation). All other cases are defined as *high-risk* medulloblastoma either on staging (residual or metastatic disease) or on high-risk biopathological criteria.

In children younger than 3 to 5 years, the low-risk category is defined by nodular desmoplastic histology or medulloblastoma with extensive nodularity, always combined with SHH pathway activation. The prognostic value of medulloblastoma with SHH pathway activation and classic histology in this age group is as yet less clear. All the other types are high-risk medulloblastoma at this age, some of them being very high risk, such as metastatic, group 3, MYC-amplified medulloblastoma.[19]

Treatment of Medulloblastoma

Standard treatment includes surgery, radiotherapy, and chemotherapy, which vary according to age at diagnosis, stage, and biopathological risk factors. Surgery aims to perform the maximum tumor resection with the fewest possible neurological sequelae, and to treat obstructive hydrocephalus if present. When hydrocephalus needs to be treated before surgery, ventriculostomy is now increasingly used rather than a ventriculo-peritoneal shunt, which carries its own morbidity. Minimum residual disease after surgery with good clinical status is preferable to complete tumor removal with impaired postoperative status, such as posterior fossa syndrome.[20] Radiotherapy of the entire craniospinal axis, with an additional local boost (today to the tumor bed rather than the entire posterior fossa[21,22]), is still part of the standard adjuvant treatment, certainly in all children older than 5 years. In younger children, radiotherapy is used depending on risk level (no radiotherapy for low-risk, focal radiotherapy for intermediate risk, or dose-adapted craniospinal radiotherapy for high-risk categories).

Chemotherapy is most often used in patients with medulloblastoma at a conventional dose. It can be the only nonsurgical treatment in young children with low-risk medulloblastoma. High-dose chemotherapy with autologous hematopoietic stem cell support can be used in patients with high-risk medulloblastoma, including young children, in order to avoid or limit the use of radiotherapy.[23,24] Overall survival (OS) and event-free survival (EFS) have improved dramatically over the past 30 years.[13] In recent studies, reported 5-year OS in standard-risk medulloblastoma was 86% to 87% and 5-year EFS was 76% to 81%.[25–28] Similar high OS and EFS rates are also observed in young children with low-risk medulloblastoma. However, OS is lower in children in the other risk categories[23,29,30] and probably different from one country to another.[31,32]

Quality of Survival Following Childhood Medulloblastoma

The tumor itself and its treatments may have devastating long-term side effects, with late-onset toxicities negatively impacting a number of domains, which in turn affect quality of survival (QoS) and persist into adulthood.[33–35] QoS is a useful term intended to integrate overall outcomes, including medical complications, cognitive deficits, psychosocial impairments in different domains (eg, academic achievement, independence, professional and social integration, activity limitations, or participation restrictions), and self-reported and/or proxy-reported quality of life.[36–41]

Aim of This Literature Review

This review aims to summarize the medical, neurocognitive, psychosocial, and quality-of-life outcomes after childhood medulloblastoma, and the risk factors (or predictors) for poor QoS. A better understanding of the determinants of QoS after childhood medulloblastoma is required in order to propose specific interventions aiming to improve QoS.

Methods

This work consists of a narrative review, rather than a systematic review. In order to retrieve the most relevant papers, the Medline database was searched from 1990 up

to April 2016. Several combinations of the following key words were used: child, childhood, cancer, brain tumor (for more general effects and outcomes) and then posterior fossa tumors and finally medulloblastoma, and these were each combined alternately with:

- outcome, long-term, quality of survival, medical, audition, endocrine, neurological, cerebellar mutism, posterior fossa syndrome, late effects
- outcome, long-term, cognitive, neuropsychological, intellectual ability, intellectual quotient, attention, working memory, memory, executive functions,
- outcome, long-term, adaptive functioning, psychosocial function, emotion, social cognition, behavior, quality of life, health-related quality of life, academic, school, independence, autonomy.

The reference lists of the papers selected were searched in order to include papers that might have been omitted. Papers were included if they reported meaningful information regarding outcome following childhood medulloblastoma in any of the domains selected (see Table 1 for a summary of the investigations of QoS in children treated for medulloblastoma). Previous literature reviews on similar topics were analyzed, but not systematically included. Finally, papers focusing on the role of the cerebellum in cognition, learning and behavior were included for the discussion.

Medical Outcomes

Overall, health status is poor and disability levels are considerable in adulthood following childhood medulloblastoma. Survivors of medulloblastoma are among those who suffer the most severe, clinically significant disabilities, with complaints and difficulties in a vast majority of patients several years postdiagnosis. Specifically, the tumor and its treatment may cause neurological and endocrine deficits, hearing loss, occurrence of secondary tumors, and other chronic conditions.[33–35]

Neurological and Motor Deficits

Persistent, long-term, disabling neurological deficits are present in a large proportion of patients following treatment for medulloblastoma. These include ataxia/ balance abnormalities and coordination disorders, fine motor function impairment and writing difficulties, cranial nerve palsies with oculomotor dysfunctions, possible facial nerve paralysis, and, less frequently, epilepsy, motor deficit (hemiparesis), or involuntary movements.[35,42–47] Fine motor functioning/manual dexterity, often assessed using tapping or pegboard tasks, are consistently impaired and significantly associated not only with ataxia, but also with intellectual ability and cognitive function.[46,48–50] In children treated for medulloblastoma, kinematic analysis of drawing and writing showed significant impairments in automation and speed.[43] These difficulties often require rehabilitation and remedial teaching, with referral to special education services or at least specific adaptations in the classroom.

Hearing Loss (Ototoxicity)

Hearing loss can be linked to the anatomical location of the tumor, although the main causes of ototoxicity are cisplatin chemotherapy and radiotherapy.[51–56] Ototoxicity increases with the combination of the 2 treatments, as radiation therapy potentiates cisplatin-induced ototoxicity when delivered concomitantly.[53,54] Hearing loss can have a profound impact on a child's quality of life, affecting not only communication skills, but also social and cognitive development.[57,58] Auditory deficits are associated with a higher degree of neurocognitive complaints in adult survivors of childhood CNS tumors.[59] This side effect can been partially reduced by changing the radiation therapy field from the entire posterior fossa to the tumor bed, by the use of intensity-modulated radiation therapy, and, more recently, by proton beam therapy, which enables radiation to be delivered to the target tissue while to some extent sparing the surrounding tissues.[55,56,60,61]

Endocrine Issues[33–35,56,62–65]

Growth deficit is caused by growth hormone deficiency, as well as by craniospinal-irradiation-induced spine shortening, especially in patients treated before the age of 3 years. Indeed, craniospinal radiotherapy affects the growth of the axial skeleton, leading to shorter standing and sitting height, with normal growth of the upper and lower extremities. In addition, chemotherapy could potentiate the deleterious effects of radiation on growth. Endocrine deficits, which occur in more than half of patients several years post-treatment, are most often centered on the hypothalamo-pituitary tract and may include growth hormone deficiency, early or delayed puberty onset, hypogonadism, reduced fertility, hypothyroidism, obesity, and, more rarely, cortisol deficiency. In a report on patients treated in infancy, 100% of the survivors displayed growth abnormalities requiring hormone replacement therapy.[29] Direct irradiation of thyroid or ovary radiation during craniospinal radiation could cause a combination of central and peripheral hormonal deficiency. Timely and ideally presymptomatic hormone replacement therapy could prevent health-related consequences of disturbed growth, as well as thyroid and gonadal deficits. Lifelong follow-up and hormone replacement should be organized whenever necessary.

Secondary Tumors

Some patients with medulloblastoma go on to develop secondary tumors, most often meningiomas and high-grade gliomas, which can be induced by radiotherapy.[34,66] Venous malformations (cavernomas) may also appear following radiation. The 10-year incidence rate of secondary malignancies has been estimated at 4.2%, and many were

Table 1 Summary of investigations of QoS in children treated for MB

Ref.	Author, year	Population (n)	Follow-up	Main findings
6	Armstrong et al., 2009	Adult survivors of childhood CNS malignancies (2821); MB (395)	≥10 years	RT increased the risk of subsequent CNS neoplasms, neurocognitive impairment, and unemployment.
42	Benesch et al., 2009	MB (18); ependymoma (5)	Md = 56 months	Neurological late effects correlated with poorer QoL in younger patients. No significant correlation between neurocognitive performance and QoL.
38	Bhat et al., 2005	BT (134); MB (32)	M = 4.26 years	RT associated with lower total scores of HRQoL (PedsQL) and psychosocial, emotional, and social functioning.
108	Bonner et al., 2008	BT (51); MB (12)	M = 6.1 years	Deficits in social functioning related to errors in facial expression recognition.
40	Brinkman et al., 2012	embryonal BT (220); MB (174)	M = 3.6 years	Parent-report: largely positive social adjustment; PFS and high-risk treatment status associated with social problems.
75	Brinkman et al., 2012	MB (20)	≥10 years	Reduced white matter integrity associated with poorer performance on tasks of executive function.
116	Bull et al., 2014	MB (37), astrocytoma (35); controls (38)	3 years	Cognitive and emotional disturbances, as well as older age at enrollment predicted lower HRQoL.
115	Bull et al., 2015	MB (37), astrocytoma (35); controls (38)	3 years	Some association of QoS measured through questionnaires with FSIQ in the whole sample.
46	Callu et al., 2009	CT (39): malignant (20) and benign (19)	≥ 6 months after end of treatment	Cerebellar signs and impaired manual skills (Purdue Pegboard) were strongly associated with cognitive difficulties and lesion of the dentate nuclei.
67	Cassidy et al., 2000	MB (24)	6 months to 7 years	Ocular sequelae: 50%; required ophthalmic intervention: 41%.
105	Catsman-Berrevoets et al., 2010	PFS (41) after resection of CT (CMS)	Until recurrence of speech	During recovery all children were dysarthric. Association of duration of mutism with severity of neurological symptoms.
118	Copeland et al., 1999	CT (27), dg ≤ 36 months; MB (15)	1 to 13 years	IQ decline in children who received cranial RT.
50	Davis et al., 2010	CT (15); MB(5); controls (242)	5 to 126 months	Correlation between cognitive and motor skills in both groups.
92	De Smet et al., 2007	Review of 283 cases of CMS	Review	Almost all children (98.8%) displayed motor speech deficits after the mute period.
137	De Smet et al., 2012	CT (24); with CMS (12)	1 to 12 years after tumor	Speech analysis revealed more severe deficits in patients with CMS.
34	Edelstein et al., 2011	MB (20)	Md = 15.5 years	Endocrine deficiencies most common and 60% hypothyroid. Secondary tumors: 25%. Diabetes, hypertension and chronic conditions interpreted as signs of early aging. Scores below average across multiple neurocognitive domains. Younger age at diagnosis was associated with lower IQ scores.
59	Ellenberg et al., 2009	Pediatric survivors of CNS tumors (802); MB (172)	≥ 16 years	Auditory deficits, radiation and female gender were associated with a higher degree of questionnaire-reported neurocognitive complaints.
33	Frange et al., 2009	MB (45)	Md = 14.4 years	Self-reported (HUI) endocrine complications: 52%; neurological deficits: 79%. Impairments in psychosocial functioning included: employment, driving capacity, independent living, and marital status in most patients.
133	Gelabert-González et al., 2001	Review of 134 cases of CMS; MB (85)	Review	Lesion of the vermis in 94% of the cases.

Table 1 Continued

Ref.	Author, year	Population (n)	Follow-up	Main findings
22	Grill et al., 1999	PF tumors (31); MB (19)	≥1 year	High craniospinal irradiation dose associated with lower FSIQ and lower verbal comprehension scores.
48	Grill et al., 2004	Malignant PF tumors (76); MB (52)	M = 5.2 years	Fine motor deficits (Purdue Pegboard) and preoperative hydrocephalus associated with low verbal IQ.
123	Gupta et al., 2012	MB (20)	2 years	Preserved cognitive function with HFRT.
138	Hardy et al., 2008	MB (35)	2 years	Lower IQ and academic skills in survivors with shunted hydrocephalus.
62	Heikens et al., 1998	MB (20)	Md = 16 years	Endocrine abnormalities: 75%; impaired growth hormone secretion: 70%.
110	Henrich et al., 2014	Parents (16) and care providers (16) of MB survivors	M = 10 years	Semi-structured interview: parents considered social functioning as the most important factor, while providers thought that parents cared most about their children's cognitive functioning.
98	Hoppe-Hirsch et al., 1995	MB (59) and ependymoma (37) with RT only in PF	10 years	Progressive IQ decline in the MB group at 5-year and 10-year follow-up.
106	Hopyan et al., 2010	CT (37); MB (18)	M = 63.7 months	CT disrupted emotional regulation through cognition control.
55	Huang et al., 2002	MB (26)	Md = 18 to 51 months	Intensity-modulated radiation therapy, compared to conventional RT (CSR followed by posterior fossa boost), reduced cisplatin ototoxicity.
104	Huber et al., 2007	PF tumors (54); MB (29)	M = 13.4 years	Ataxic dysarthric speech in irradiated MB survivors. Disfluent and slow speech, regardless of tumor type and irradiation history.
36	Johnson et al., 1994	MB (32)	≥5 years	Lower IQ for patients diagnosed before the age of 3 years.
140	Kao et al., 1994	MB/PNET (28)	Pre- and post-treatment	Adverse perioperative medical events associated with neurocognitive deterioration
37	Kennedy et al., 2014	MB (151)	Md = 5.8 years	HFRT associated with better reports of executive function (BRIEF) and poorer growth compared with STRT. Hair abnormalities: 80%.
120	Kieffer-Renaux et al., 2000	MB (36)	M = 4.3 years	Supratentorial radiation dose associated with impaired intellectual outcome.
97	Kieffer-Renaux et al., 2005	PF tumors (40); MB (31)	M = 6.7 years	Decline of FSIQ over time, except in case of posterior fossa RT alone (n=7).
41	Kiltie et al., 1997	Young MB, dg < 36 months (37)	≥10 years	Stable employment maintenance was rare (n=1) and no young adult was married.
114	Kuhlthau et al., 2012	BT (142); MB (50) treated with proton RT	3 years	Poor parent-reported HRQoL in children with MB. HRQoL negatively correlated with CSR and chemotherapy and positively associated with FSIQ.
112	Kulkarni et al., 2013	PF (62); MB (19)	M = 5.2 years	QoL similar to the general population. Decreased QoL associated with: hydrocephalus, ventricular size, poor family functioning, and family income.
122	Lafay-Cousin et al., 2009	MB, <3 years of age or less (29)	≥5 years	Low IQ and academic performances associated with conventional RT, but not with reduced RT.
52	Lafay-Cousin et al., 2013	MB (35)	Md = 67 months	Cisplatin ototoxicity requiring hearing aid in 25.7% of patients.
63	Laughton et al., 2008	Embryonal BT (88); MB (75)	4 years	Growth hormone deficiency: 93%, thyroid-stimulation deficiency: 23%, adrenocorticotropic deficiency: 38%, and primary hypothyroidism: 65%.

Table 1 Continued

Ref.	Author, year	Population (n)	Follow-up	Main findings
136	Law et al., 2012	PF tumors (51); MB and CMS (38)	M = 3.5 years	CMS associated with left-handedness, MB histology and damage within the cerebello-thalamo-cerebral pathway in the right cerebellum.
90	Law et al., 2015	MB (24); controls (20)	M = 6.28 years	Compromised cerebrocerebellar connections associated with deficits in working memory.
78	Levisohn et al., 2000	CT (19); MB (11)	Testing prior to radiation (if required)	"Cerebellar cognitive affective syndrome": impairments in executive and visuospatial functions, expressive language, verbal memory and affect modulation.
64	Livesey et al., 1990	BT (144); MB (60)	Md = 9.6 years	Growth hormone deficiency: 97%. Effect of spinal irradiation on spinal growth.
124	Mabbott et al., 2005	PF tumors (53); MB (46)	Md = 4.84 years	Decline in academic abilities. Hydrocephalus associated with poorer academic achievement. Neither psychological distress nor behavior problems were significant.
74	Mabbott et al., 2006	MB (8)	M = 2.5 years	Microscopic damage in white matter related to poor intellectual outcome.
87	Mabbott et al., 2008	PF tumors (64); cranial radiation in majority MB (32)	M = 4.59 years	Sustained attention and working memory largely intact. Slow processing speed and low IQ associated with cranial RT and post-surgical complications.
89	Mabbott et al., 2009	PF tumors (39); MB (11) and non-CNS tumors (15)	M = 4.98 years	Deficits in selective attention in all patients with PF tumors.
100	Maddrey et al., 2005	MB (16)	M = 15 years	Significant impairments in more than 50% of survivors in attention, memory, visuospatial abilities, motor function, language, and executive functioning. Impairments in all psychosocial domains. Self-reported and caregiver-reported QoL in the normal range.
135	Miller et al., 2010	CT (22); PFS (11)	3 to 4 weeks	PFS associated with bilateral damage to the proximal efferent cerebellar pathway.
60	Moeller et al., 2011	MB receiving proton therapy (23)	1 year	Lower ototoxicity associated with the use of proton therapy.
95	Moxon-Emre et al., 2014	MB (113)	M = 6.06 years	No intellectual declines associated with reduced-dose CSR plus TB boost. Poorer intellectual outcomes associated with complications, hydrocephalus, and CMS.
94	Mulhern et al., 1998	MB (22)	6.1 to 9.9 years	IQ lower in younger children at diagnosis (less than 8.45 years) who were treated with standard-dose cranial RT, compared with reduced-dose cranial RT.
72	Mulhern et al., 1999	MB (18); low-grade PF tumors (18)	≥1 year	Low FSIQ associated with reduced volume of normal white matter.
73	Mulhern et al., 2001	Pediatric MB (42)	≥1 year	Worse neurocognitive outcome associated with young age at CSR, longer time since completion of treatment and white matter loss.
119	Mulhern et al., 2005	MB (111)	Md = 3.14 years	Significant decline in mean IQ and academic skills. Higher rates of decline in high-risk patients younger at diagnosis (<7 years).
71	Odame et al., 2006	PF tumors (25); MB (7)	≥ 1 year	Osteoporosis in more than 40% of patients who received RT.
65	Olshan et al., 1992	MB (38)	4 years	Chemotherapy potentiates the deleterious effects of RT on growth.
58	Orgel et al., 2016	BT with platinum therapy (58); MB (39)	M = 4.6 years	Hearing loss in 55% of patients associated with deficits in intelligence, executive function, and verbal reasoning.

Table 1 Continued

Ref.	Author, year	Population (n)	Follow-up	Main findings
134	Ozimek et al., 2004	CT (14); MB (3)	Postoperative period	Association of CMS with lesion to the deep cerebellar nuclei
26	Packer et al., 2013	MB (379)	Md = 9.7 years	Estimated cumulative 10-year incidence rate of secondary malignancies = 4.2%.
99	Palmer et al., 2001	MB (44)	M = 5.24 years	Decline on FSIQ (2.55 points/yr) but increased raw scores (not age-adjusted).
93	Palmer et al., 2003	MB (50)	7 years	CSR (35–40 Gy) associated with IQ decline of about 2 points/yr.
132	Palmer et al., 2010	MB (44); MB with CMS (22)	1 year	CMS associated with lower processing speed, attention, working memory, cognitive efficiency, and academic skills.
86	Palmer et al., 2013	MB (126)	5 years	Associations: Poor processing speed with younger age at diagnosis and high-risk; poor working memory and poor broad attention with high-risk; parental education and marital status with baseline scores of working memory and broad attention.
54	Paulino et al., 2010	MB (44)	Md = 41 months	Severe ototoxicity in 18.2% of children treated with intensity-modulated radiation therapy boost and cisplatin-based chemotherapy.
44	Piscione et al., 2014	PF tumors (30); MB (12)	M = 6.1 years	Decreased functioning in balance and running speed ability.
49	Puget et al., 2009	PF tumors (61); MB (50)	M = 5.6 years	Neurological deficits were strong predictors of low cognitive performances and were associated with damage to the dentate nuclei or the inferior vermis.
61	Pulsifer at al, 2015	CNS tumor survivors treated with proton RT (60); MB (23)	M = 2.5 years	Proton radiation therapy associated with decline in processing speed scores, but not with significant changes in FSIQ and other IQ components.
76	Reddick et al., 2003	BT (40); MB (18)	Md = 5.7 years	Reduced normal-appearing white matter associated with decreased attentional abilities, leading to decline in IQ and academic achievement.
88	Reeves et al., 2005	MB (38)	M = 1.97 years	Attention deficits (Conners Continuous Performance Test). No deficits in Verbal IQ.
35	Ribi et al., 2005	MB survivors (18)	M = 12.2 years	Neurological complications: 72%. Endocrine deficits: 61%. Neurocognitive deficits: attention and processing speed: 79%; learning and memory: 88%; language: 56%; visual perception: 50%; executive functions: 64%.
96	Ris et al., 2001	MB (43)	Md = 2.5 years	IQ decline steeper in younger children and females.
83	Ris et al., 2013	MB (110)	≥5 years	Decline in academic and intellectual performances; steeper decline in younger patients. CMS associated with lower IQ.
129	Riva et al., 2000	CT (26); MB (11)	5 to 6 weeks after surgery (prior to radiation)	Left CT: language and auditory sequential memory deficits; right CT: visuospatial deficits; vermian lesions: postsurgical CMS or behavior disturbances.
130	Robertson et al., 2006	MB (450)	≥ 1 year	CMS in 24% of the children, associated with brainstem invasion.
139	Roncadin et al., 2008	PF tumors (58); MB (29)	5 years	Poor outcome associated with adverse perioperative medical events.
79	Rønning et al., 2005	PF tumors (23); MB (11)	>10 years	Young age at time of treatment associated with lower IQ in the MB group.
43	Rueckriegel et al., 2009	MB (27) and astrocytoma (16)	≥ 1 year	Loss of fine motor function and ataxia associated with lower IQ.

Table 1 Continued

Ref.	Author, year	Population (n)	Follow-up	Main findings
45	Schoch et al., 2006	CT (22); malignant (8)	M = 7.7 years	Balance abnormalities associated with involvement of the deep cerebellar nuclei.
84	Schreiber et al., 2014	MB (165)	Up to 5 years	Decline in intellectual and academic skills associated with hearing loss, PFS, and young age at diagnosis.
121	Silber et al., 1992	MB (24); ALL (24)	M = 3.65 years	Final IQ associated with initial IQ, RT dose, and age at RT.
82	Spiegler et al., 2004	PF tumors (34); MB (30)	Up to 120 months	Declines in IQ, visual-motor integration, visual memory, verbal fluency, and executive functioning.
47	Ullrich et al., 2015	MB (52)	M = 7.5 years	Incidence of seizures: 7.7%.
80	Vaquero et al., 2008	CT (20); MB (7)	M = 6.5 years	Impaired executive functioning.
29	Walter et al., 1999	Young MB (29)	≥ 5 years	IQ decline. Required hormone replacement therapy = 100%.
131	Wells et al., 2010	MB (28); CMS (11)	1 year	CMS associated with brainstem invasion, superior and middle cerebellar peduncle edema, and poorer functional outcomes.
70	Wolfe et al., 2012	PF tumor (14); MB (10)	≥ 2 years	Impaired cardio–respiratory fitness.
56	Yock, 2016	MB proton RT (49)	Md = 7 years	FSIQ decline driven by decrements in processing speed and verbal comprehension.

ALL: acute lymphocytic leukemia; BRIEF: Behavior Rating Inventory of Executive Function; BT: brain tumors; CMS: cerebellar mutism syndrome; CNS: central nervous system; CSR: craniospinal radiation; CT: cerebellar tumors; Dg: diagnosis; FSIQ: Full Scale Intelligence Quotient; HFRT: hyperfractionated radiation therapy; HRQoL: health-related quality of life; HUI: Health Utilities Index; IQ: intelligence quotient; M: mean; MB: medulloblastoma; Md: median; PF: posterior fossa; PFS: posterior fossa syndrome; PNET: primitive neuroectodermal tumor; QoL: quality of life; STRT: standard radiation therapy; TB: tumor bed; RT: radiotherapy; Yr: year.

malignant gliomas.[26] Patients with genetic predisposition are at higher risk of a second cancer.[66]

Other Medical Outcomes

Ophthalmic complications are frequent and visual loss or blindness may occur, especially in case of delayed diagnosis, as a result of prolonged, increased intracranial pressure.[67–69] Radiation-induced cataract may also impair vision and require surgery. According to one report, adult survivors of childhood medulloblastoma could present increased risk of chronic pathologies such as diabetes and hypertension, both of which are related to early aging.[34] Reduced cardio–respiratory fitness in patients treated for posterior fossa tumors has been reported, as a result of a combination of factors related to the tumor and its treatments, as well as to lower rates of physical exercise.[70] Osteoporosis, associated with higher levels of pain, lower levels of mobility, and reduced overall health-related quality of life (HRQoL), has also been reported in over 40% of children treated with radiation therapy for brain tumors.[71] Patients also often complain about persistent alopecia, which can be severe.[37]

Cognitive Outcome

Patients treated for childhood medulloblastoma often present significant cognitive deficits and academic difficulties requiring special education services.[8,34,35] These problems are thought to be related to the effects of radiation on subsequent white matter development[72–76] and to cerebellar damage.[46,48,49,77–81] Intellectual ability, measured through the intelligence quotient (IQ), is the most frequently studied outcome.[82–85] Deficits are reported in most cognitive domains, with an emphasis on attention, processing speed, and working memory.[86–90] Executive function deficits are frequent and are attributed to cerebello-cerebral pathway dysfunction.[91] Motor speech deficits were reported in almost all survivors following postoperative posterior fossa syndrome.[92] The association between fine motor skill impairment and signs of cerebellar dysfunction on one hand, and cognitive function on the other, was found to be significant and strong.[46,48–50] Many adults treated for pediatric medulloblastoma exhibit global neurocognitive impairments many years postdiagnosis, with performances falling within the clinical range in several cognitive domains.[34]

Intellectual Functioning

A deleterious impact of the tumor and its treatments on IQ is commonly reported, with decline over time during at least the first 7 years.[22,93–98] Patients who were younger at diagnosis are at higher risk of impaired cognitive functioning.[29,85,93] The observed decline is frequently much steeper in children with higher IQ scores at the first assessment.[93,98] This decline starts in the first years following completion of treatment,[93] while a particularly long-term study[34] reported

stability of IQ scores 20 to 40 years postdiagnosis. The decrease in IQ scores has been attributed to slower acquisition of knowledge (with children acquiring knowledge at 50% to 60% the expected rate), rather than to the loss of previously learned information, as indicated by raw score instead of the usual age-adjusted score analysis.[99]

Attention, Working Memory, and Processing Speed

Although deficits have been documented in a variety of cognitive functions, impairments have most often been identified in sustained attention (the ability to remain alert or focused), information processing speed, and working memory.[86–91,100] Processing speed is typically conceptualized as the rapidity with which one can perform relatively automatic mental tasks. Working memory, usually conceptualized as an executive function, is a temporary workspace in which information is maintained and manipulated over a short period. Faster processing speed probably places less demand on maintaining information in the working memory. These cognitive functions are important for skill and knowledge acquisition, and their dysfunction has been hypothesized to be the core deficit explaining the IQ decline and academic underachievement.[85,86]

Executive Functions

Executive functions are a collection of distinct, although inter-related, abilities that are necessary for effective and appropriate behavior and for independent functioning. These include inhibition, mental flexibility, planning, decision-making, judgment, abstract reasoning, concept formation, problem-solving, and awareness. Significant deficits among patients with medulloblastoma have been reported in most of these areas, with deteriorating performances over time.[81,100] Metacognition and awareness difficulties have also been reported in these patients, with unrealistic perceptions of their intellectual and scholastic abilities.[37] Executive functions are most often assessed using paper-and-pencil tests, which do not always reflect the actual difficulties patients can experience in everyday life. Therefore, a number of more "ecological" assessments have been developed, which include tests mimicking activities of everyday life in a formal testing environment and questionnaires focusing on executive deficits that can be observed in daily situations (see,[101] for a review). However, the degree of impairment in executive functioning assessed by questionnaires is often low when compared with that obtained by direct neuropsychological testing, and correlations between questionnaires and performance-based measures are generally fairly poor.[102,103]

Speech and Language

Cerebellar tumor survivors may present disfluent and slow speech and medulloblastoma survivors can be at risk for exhibiting ataxic dysarthric features.[104] Following cerebellar mutism syndrome, motor speech and language deficits have been reported.[105] According to one investigation, motor speech deficits could be present in almost all (98.8 %) patients who sustained this complication.[92]

Other Cognitive Outcomes

Memory and learning deficits were reported in a majority of children with medulloblastoma,[35] as well as significant declines in visual-motor integration, visual memory, and verbal fluency, but not in verbal memory and receptive vocabulary.[82] Another investigation reported relative insensitivity to negative emotions and difficulties in cognitive control of emotions in patients treated for medulloblastoma.[106]

Psychosocial Functioning and Quality of Life

Compared to healthy controls or to subjects with non-CNS pediatric malignancies, children treated for medulloblastoma show an increased risk for academic underachievement and need for remedial teaching,[9–11,100] unemployment,[2,12,41,59] for not being married or having children,[2,33,41] inability to live independently[33,100] and social isolation.[35,100] A meta-analysis of unemployment among adult survivors of childhood cancers showed that survivors were nearly twice as likely to be unemployed than healthy controls, and 5 times more likely in case of brain tumor; the risk of unemployment increased further in case of cranial radiotherapy.[12] It has been repeatedly reported that, among adult survivors of childhood cancer, only those who have had CNS tumors experience significant educational deficits, especially when treatment included cranial irradiation.[9–11,107] Hearing loss[2,59] and specific neuropsychological deficits, such as impairment of facial expression recognition,[108] increase the risk of poor social outcome.

Studies using questionnaires assessing social adjustment among childhood brain tumor survivors, completed either by the survivor or the parents, have indicated conflicting results, although social isolation (eg, having fewer friends) is consistently reported (see[39] and [109] for reviews). A recent study using parental questionnaires concluded that parent ratings of their child's social adjustment several years after a pediatric embryonal tumor were largely positive.[40] Another study showed that parents of children treated for medulloblastoma considered that the most important factor in their child's quality of life was social functioning (eg, ability to make friends); conversely, health care providers thought that parents were mainly concerned about their children's cognitive functioning and academic achievement.[110]

Other studies found that self-reported quality of life was not related to the degree of disability.[111] HRQoL is a multidimensional concept referring specifically to the subjective view of the individual survivor about his or her life situation. It includes physical, social, cognitive, and emotional functioning dimensions and is emerging as an essential health outcome for brain tumor clinical trials.[38] In a study on adolescent and adult survivors of childhood cancer,

HRQoL differences between survivors and controls were small, but having had a CNS tumor was associated with lower HRQoL.[5] According to some studies of childhood medulloblastoma survivors, despite the frequent, severe neuropsychological and functional deficits described above, HRQoL reported by both the survivors and their caregivers was within the normal range[100,112] and/or was not related to psychometric measures.[113] However, other studies have found significantly decreased self-reported and proxy-reported HRQoL among patients with brain tumors, especially patients with medulloblastoma,[38,114] and some degree of relationship between psychometric measures and self-reported and proxy-reported HRQoL.[115,116] HRQoL tends to be relatively higher according to self-reports than to proxy (parent) reports, although the two are frequently correlated.[35,114]

Factors Associated with Quality of Survival

Factors associated with overall QoS in children treated for medulloblastoma include: age at diagnosis; treatment-related factors: surgery (eg, perioperative and postsurgery medical events and complications), radiotherapy (doses and volumes), chemotherapy (eg, cisplatin-induced hearing loss); tumor-related factors (standard or high-risk, size, localization within the cerebellum, brainstem involvement, hydrocephalus, medulloblastoma subgroup, and biological markers); presence of a postoperative cerebellar mutism syndrome; presence of persistent neurological, fine motor, or sensory deficits (eg, ataxia, manual dexterity impairment, dysarthria, and oculomotor and visual deficits); factors related to child, family, and environment (gender, age, parental education level and socioeconomic status, educational environment, and rehabilitation interventions). The list of associated factors can differ according to the specific outcome considered (medical, neurocognitive, or psychosocial). For instance, neurological, sensory, endocrine, and neurocognitive deficits could be risk factors for social isolation, while motor deficits could be more strongly associated with cognitive problems. In addition, respondent's individual personality and emotional factors, as well as contextual factors (eg, respondent's understanding of the aims of the questionnaires), can influence the answers to questionnaires assessing social adjustment or quality of life.[103]

Radiotherapy

Radiotherapy is probably the most widely investigated risk factor for poor QoS among children with medulloblastoma. Radiotherapy is the main risk factor for occurrence of secondary tumors[6,26] and cranial radiation therapy is a major factor for endocrine deficits[117] and hearing loss,[53–55] especially in young patients.[53,63,117] Although the idea that only children who receive cranial radiation therapy suffer neurocognitive deficits[118] is now questioned by evidence that the cerebellar lesion may itself play an important role (eg,[49]). Many studies have shown the negative impact of cranial radiation therapy on cognition,[72,73,97,98,118,119] as well as an increase in neurocognitive deficits with an increase in dose.[22,95,99,120–122] Cognitive deficits have been associated with white matter loss[72,73,75,76] and with microscopic damage of normally appearing white matter after cranial radiation therapy.[74] Neurocognitive deficits have been mainly attributed to supratentorial irradiation and much less to posterior fossa irradiation.[97,98,120] However, a recent study reported stable intellectual trajectories in patients treated with reduced craniospinal irradiation plus tumor bed boost, contrasting with the intellectual declines usually observed in patients treated with reduced craniospinal irradiation plus posterior fossa boost.[95] Another study reported cognitive impairment even after posterior fossa irradiation alone. Cranial radiation therapy was found to be associated with poor educational outcomes,[9,11,107] but less systematically with reduced social adjustment or quality of life.[39,40,114] New therapeutic protocols, using proton beam therapy[56,61,114] or hyperfractionated radiation therapy,[37,123] aim to reduce the negative effects of conventional radiation therapy.

Age at Diagnosis

Young age at diagnosis (less than 3 or 5 years) is one of the classification criteria for high-risk medulloblastoma and one of the most regularly observed risk factors for neurocognitive deficits and IQ decline, especially in case of cranial radiation therapy.[8,80,84,86,93,94,111,124] According to one report, following conventional craniospinal irradiation (35 to 40 Gy), an immediate loss of intellectual performance is observed in younger patients, whereas older patients demonstrate a delay prior to decline in performance.[93] There is less evidence regarding the association between young age at diagnosis and reported social adjustment and quality of life.[39,116]

Role and Topography of Cerebellar Injury

There is much evidence that cerebellar lesions can cause cognitive dysfunctions (eg,[125–127]), such as working memory deficits,[128] and the "cerebellar cognitive affective syndrome" described in adults[77] has also been reported in children after resection of cerebellar tumors.[78] Different neuropsychological deficits have been described according to the laterality of the cerebellar lesion: language processing deficits have been associated with right cerebellar tumors; spatial and visual deficits have been reported with left cerebellar tumors; and cerebellar mutism syndrome and/or behavioral disturbances have been described with vermian lesions.[129] However, these specific profiles were described in a small sample of patients with posterior fossa tumors, without long-term follow-up. Psychological and behavior problems were not a significant concern in patients treated for medulloblastoma,[124] a tumor which generally involves the vermis. On the other hand, cognitive deficits have been described in children following surgery (without radiotherapy and chemotherapy) for benign cerebellar tumors[81] and there is evidence

that lesions of the cerebellar nuclei are strongly associated with more severe cognitive and motor deficits,[46,49] as well as with the occurrence of a cerebellar mutism syndrome.

Cerebellar Mutism Syndrome

One frequent complication of surgery is cerebellar mutism syndrome, also known as posterior fossa syndrome. It affects approximately 25% of patients after surgery.[92,130–133] The occurrence of cerebellar mutism syndrome has been associated with disruption of the cerebellocerebral connections.[133–135] Left-handedness and disruption of the connection between the right cerebellum and the left frontal cortex have also been reported as risk factors for the occurrence of postsurgical cerebellar mutism syndrome.[135] The presence of cerebellar mutism syndrome was associated with increased risk of persistent ataxia and cerebellar dysfunction signs,[105,130] speech disturbances,[92,136,137] lower IQ,[84,95] lower academic performances,[84,132] and lower processing speed, attention, and executive functions[132] in the long term.

Hydrocephalus

Preoperative hydrocephalus was associated with lower verbal IQ in one report,[48] and hydrocephalus requiring permanent shunting has been reported to be associated with lower IQ,[138] lower academic abilities,[124,138] and more reported difficulties in neurocognitive functions,[59] social adjustment,[39] and quality of life.[112]

Adverse Perioperative Medical Events and Postsurgical Complications

Perioperative and postsurgical complications (eg, infections, hemorrhagic complications, repeat surgery) can lead to poor neurological, intellectual, and social outcomes.[87,95,139,140]

Hearing Loss

Hearing loss could be a significant risk factor for decline in intellectual and academic skills,[84] as well as a risk factor for poor social outcome.[2]

Gender

Female gender was reported as a risk factor for verbal IQ decline in children treated for medulloblastoma,[96] for self-reported neurocognitive impairment among survivors of CNS malignancies,[59] for poor educational outcome among survivors of childhood cancer[9–11] and survivors of pediatric brain tumors,[107] as well as for lower HRQoL in survivors of pediatric medulloblastoma.[37] Despite these reports, there is no clear explanation of this often-cited disadvantage of female gender in cognition and academic achievement after childhood cancer or brain tumor.

Family and Environmental Factors

Previous investigations of QoS following diagnosis of pediatric medulloblastoma have occasionally taken into account family and environmental factors. A few studies have reported that the parents' educational level and marital status were significantly associated with IQ, broad attention, or working memory baseline scores, but not with change over time.[86,93] Socioeconomic status and family functioning were also reported as factors associated with social adjustment or quality of life.[5,39]

Concluding Remarks and Future Directions

Determinants of poor QoS after childhood medulloblastoma are relatively clear for medical problems, neurocognitive outcomes, and situation-based social difficulties (academic underachievement, unemployment, absence of marital or parental status, absence of independence, etc.). Young age at diagnosis and treatment, conventional radiotherapy, perioperative adverse medical events, tumor and surgery-induced cerebello-cerebral disconnection probably leading to postsurgical cerebellar mutism syndrome and neurological abnormalities, and hearing loss are the main factors compromising these aspects of QoS.

The results are more conflicting for risk factors for poor self-reported and proxy-reported (ie, questionnaire-based) social adjustment and quality of life, with a frequent lack of concordance between questionnaire results and performance-based or patient situation-based assessments. This lack of concordance simply confirms the clinical observation that patients and/or proxies completing questionnaires may minimize or deny considerable difficulties or, on the contrary, maximize minor difficulties or express worries about problems that are not actually present. It is important to take discrepancies of this sort into account for rehabilitation interventions requiring close collaboration of the patient and the proxies, and assessments should include both performance-based assessments and questionnaires.

Interventions aiming to improve neurocognitive outcomes require an understanding of the nature of the almost systematically reported intellectual decline after treatment of childhood medulloblastoma. Logically, decline in performance can be steeper when the baseline performance is high compared to when it is low, and, in case of progressive decline, time since completion of treatment correlates negatively with final performance. Descriptions of decline in terms of "*x* points per year" should be interpreted with caution, as the effect of time is not linear. Furthermore, initial performances should be taken into account when interpreting the consequences of the decline: when initial performances are different, but slopes are identical, as it has been reported for parental educational level for instance,[86,93] declines in percentages are different (eg, a 10-point difference is an 8% decline if the initial score is 120, but a 14% decline if it is 70).

Slow processing speed and working memory and attention deficits are considered to be the "core" cognitive deficits in children treated for medulloblastoma, explaining

the IQ decline and academic underachievement; however, this is without clear reference to the cerebellar damage itself.[85] It is important to note that the same core deficits are expected after cerebellar lesions, given the role of the cerebellum in working memory[128] and, more generally, in automatic processing.[141,142] A difficulty establishing motor and cognitive automatisms could lead to slower processing and excessive demands placed on attention. Thus, if attention difficulties are related to the absence of automation due to cerebellar dysfunction, they could probably be interpreted as an increased attentional demand.

Manual skill impairments and oculomotor or articulatory deficits, clearly cerebellum-dependent, are strongly associated with cognitive deficits in children treated for medulloblastoma. As already suggested by some authors who have criticized the "cerebellar cognitive affective syndrome" (eg,[143]), it may be difficult to propose a clear distinction between the motor and cognitive functions of the cerebellum, if one considers, for instance, the articulatory movements involved in the subvocal rehearsal of verbal working memory, or the oculomotor movements implicated in spatial and visual sequential memory. Neurological and sensory abnormalities detected in careful clinical examination after the end of treatments for childhood medulloblastoma should be considered as a major risk factor for subsequent cognitive difficulties.

The respective roles of radiotherapy-induced white matter abnormalities on the one hand, and of cerebellar injury, on the other, in cognitive impairment remain unclear. Widespread alterations in white matter microstructure have recently been reported in adults following resection (without radiotherapy) of pediatric low-grade cerebellar tumors.[81] Future studies should focus on specific cognitive deficits and changes in brain structure after resection of childhood benign cerebellar tumors, after posterior fossa irradiation alone, or after supratentorial irradiation alone. It is important to determine whether one or several core cognitive deficits (eg, processing speed, attention) explain the intellectual decline and have a negative impact on different cognitive domains; similarly, it is also essential to gain better understanding of the relationship between core cognitive deficits and the cerebellar lesion.

After childhood medulloblastoma, the presence or not of a "cerebellar cognitive affective syndrome"[77,78] remains unclear, especially its "affective" component. The assessment of affective and emotional difficulties needs to take into account the period in which the evaluation takes place (perioperative vs. long-term follow-up). It seems particularly important to clarify the role of vermian injuries and cerebellocerebral disconnections on behavior. For instance, on the one hand, some reports have described the behavior of children with cerebellar mutism syndrome as autism,[105] and disconnection between the right cerebellum and the supratentorial language areas has been reported in children with autism spectrum disorders.[144] On the other hand, psychological and behavioral problems are frequently reported to be not significant following medulloblastoma diagnois.[124]

Despite the large corpus of medulloblastoma studies, some implications of the disease and its treatments remain understudied and are characterized by inconclusive or disputed evidence. Past research has been mainly conducted in small, heterogeneous samples and has focused on specific physiopathological entities of medulloblastoma (unicentric), as opposed to a multicentric approach, thus hindering any comparative methodology across the diversity of medulloblastoma consequences. These limitations have led researchers to recognize the importance of developing randomized controlled trials with large sample sizes, which adopt a multicentric and comparative methodology, and include comprehensive information regarding several dimensions of survivor functioning, based on direct assessments of patients and on indirect measures using patient and proxy (eg, parents, teachers) reports. Recent efforts have been developed among European countries in order to establish a consensus regarding the assessments to be performed when evaluating QoS.[115,145,146] Although these studies entail challenging organization and cooperation among different countries, they have the potential to ensure the formation of large, comparable samples from which multidomain and multi-informant data can be derived.

Future studies should investigate the associations between recent advances in molecular neuro-oncology and QoS after childhood medulloblastoma. They should also aim to uncover the nature of certain relationships, such as that between female gender and lower cognitive and academic achievement after childhood cancer or brain tumor. Likewise, the role of environmental factors, in particular family factors, on cognitive and psychosocial outcomes, which have been shown to be important in other acquired brain pathologies, such as traumatic brain injury, remains underexplored in childhood brain tumors. This is illustrated by reports on children showing positive QoS despite the presence of numerous risk factors for poor outcomes.

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