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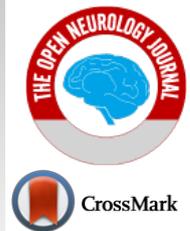
REVIEW ARTICLE

Treatment and Long-Term Sequelae in Childhood Brain Tumors

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Abstract:

In children treated for brain tumors, important deficits in cognitive development have been described. The reduction of Intelligence Quotient (IQ) is correlated with multiple conditions such as tumor location, obstructive hydrocephalus, surgical intervention, and above all, the use of radiotherapy, especially in young children. Demyelinization represents the most striking microscopic alteration following radiation: cerebral white matter's loss and failure to white matter development could partly account for changes in IQ score.

Recently, combined chemo-radiotherapeutic approaches and the improvement of radiotherapy techniques have enabled the reduction of neurocognitive symptoms and improved the standard of life of childhood brain tumor survivors.

Keywords: Children, Brain tumors, Neurocognitive deficit, Radiotherapy, IQ score, Young childrens, Radiation.

1. INTRODUCTION

Tumors of the Central Nervous System (CNS) are the most incident form among solid tumors in childhood, accounting for 20% of all pediatric malignancies [1, 2]. The brain tumors are present in two different stages of children and adolescents' life: in the first decade of life (value of 2.2-2.5 cases per 100 000 children/yr) with a major incidence of CNS embryonal tumors and ependymomas located in the posterior fossa; and the greatest number of cases have been reported in the late adolescence and early adulthood, with a major incidence of glial tumors, especially in the supratentorial compartment [3 - 5]. Surgical resection and focal or Craniospinal Irradiation (CSI), followed or not by systemic chemotherapy have been necessary for the majority of children who have survived brain tumors [6, 7].

Due to the increased aggressiveness of therapy and, in particular, of the use of radiotherapy, the survival of children treated for cancer continues to improve. Nevertheless, recent studies have shown that the treatment of brain tumors exposed the children to increased risk of reduction of quality life and cognitive development, which are described particularly following the treatment for posterior fossa tumors.

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Variables associated with increased risk of neurocognitive impairment include tumor location, obstructive hydrocephalus, surgical complications, treatment with cranial radiation, radiotherapy dose, the quantity of cerebral parenchyma that receives treatment, and younger age at diagnosis [8]. Nevertheless, recently, the improvement of radiotherapy techniques has reduced the risk of neurocognitive sequelae [1, 9, 10].

2. NEUROCOGNITIVE LATE EFFECTS

The delayed effects on neurocognitive abilities in children treated for brain tumors are frequent and debilitating.

The Intelligence Quotient (IQ) measure is generally adopted to evidence the neurocognitive effects, with a mean score of 100 and standard deviations of 15 or 16. A reduction in IQ frequently determines a decrease in basic academic achievement [9 - 12]. A few studies conducted to examine visual perceptual abilities in children affected by brain tumors reported potential difficulties in perceptual-motor, fine motor coordination, and visual-constructive abilities [13, 14].

Deficits in visual-motor and visual-spatial skills [15] and perceptual- organizational skills have also been reported [16]. A cross-sectional study demonstrated an altered performance in all neurocognitive measures of memory, attention, intellect, and academic achievement [17]. Moreover, Hirsch *et al*.

compared a series of children irradiated for medulloblastoma in the whole CNS with a series of children treated with surgery alone for a cerebellar astrocytoma [18].

Global IQ exceeded 90 in 2 and 62%, respectively, writing and reading were altered in 82 and 37%, and behavior was affected in 93 and 59%. School performance was severely compromised in 75 and 27%, respectively. In general, these studies underline at the young age when radiotherapy should be done, and the high dose of radiotherapy and the increased time from radiotherapy are the elements that, similarly to IQ, determine the most severe core deficits in the core areas of attention, memory, and academic achievement.

2.1. Principal Risk Factors for Cognitive Impairment

The nature and severity of the intellectual outcomes of children with malignant brain tumors may be related to multiple factors (Table **1**).

Table 1. Principal risk factors for cognitive impairment in children with brain tumors.

RISK FACTORS	REFERENCES
Tumor-related risk factors Location Hydrocephalus	[19,20,21]
Patient-related risk factors Age at diagnosis Neurofibromatosis type 1	[22,23,24]
Treatment-related factors Surgical complications Irradiation Doses of irradiation Volume of irradiation	[25,26][24][18,27][25,28]

2.1.1. Tumour Location

is a crucial factor that causes selective site-dependent deficits. Furthermore, some locations are at greater neurodevelopmental risk than others: a major cognitive impairment is evidenced in supratentorial tumors than infratentorial tumors, even when whole-brain radiation is not performed [29]. Besides, Ellenberg *et al.* have confirmed that greater cognitive impairment is related to hemispheric tumors.

Left hemispheric lesions are related to verbal or language-based deficits while lesions in the right hemisphere determine visual perceptual deficits [30]. Although fourth ventricle tumors are related to significant declines of IQ, the major reduction of IQ is present in hemispheric tumors than that of the third or fourth ventricle.

2.1.2. Obstructive Hydrocephalus

also plays a role in long-term outcomes for childhood brain tumors survivors. It can be the cause of the persistent headache and rapid neurological deterioration if a lumbar puncture is performed [31 - 34].

The role of intracranial hypertension in children with brain tumors has been studied mainly in children with posterior fossa tumors and it has been found that, since both children with medulloblastomas and astrocytomas suffer from hypertension but only the former are intellectually deficient, the deficits are

caused not by hypertension but by the combination of radio- and chemotherapy [18, 35]. It is important to add that the main factor responsible for the mental deterioration in hydrocephalic children is the level of intracranial pressure and, above all, the duration of the pressure on the fibers of the white matter (which causes a deficit in information processing) and of the frontal lobes, which are particularly vulnerable because of their internal complexity [35].

2.1.3. Surgical Intervention

Unless it causes direct or indirect complications, does not add any further damage to those already existing and secondary to the lesion site. Although the adoption of computer-guided neurosurgical techniques enhances the success of the operation, the choice of some anatomical approaches rather than others may lead to selective deficits [36]. For example, the prolonged retraction of the frontal lobes to reach tumors located elsewhere (e.g., craniopharyngiomas) cause complex deficits because of the internal complexity of these lobes [37].

Moreover, particular care must be taken when approaching posterior fossa tumors: the incision or destruction of the cerebellar vermis causes complex alterations in social and communicative behavior that may even reach to the extent of autism [20].

2.1.4. Radiotherapy

Many studies have focused on the sequelae on neuropsychologic functioning in pediatric brain tumor survivors [38]. In one study of 56 childhood brain tumor survivors in whom 22 received radiation therapy, 68% of survivors who received radiation treatment were characterized by IQ scores less than 90, compared with 18% who were not treated with radiotherapy [19].

Moreover, in an important neuropsychological evaluation, by Grill *et al.*, 31 children, aged 5-15 years, who were treated with radiotherapy for Posterior Fossa (PF) tumors and who had no therapy for at least 1 years, were analyzed retrospectively. Three different subgroups, with 11, 11, and 9 patients were created according to the CSI doses: 0 Gy [*i.e.*, PF irradiation only], 25 Gy, and 35 Gy, respectively. In all these cases, long-term cognitive impairment was present in most of the patients, even after PF irradiation only. A relationship between the dose of irradiation and the full-scale IQ (FSIQ) is demonstrated by the mean FSIQ scores at 84.5 (SD 5 14.0), 76.9 (SD 5 16.6), and 63.7 (SD 5 15.4) for 0 Gy, 25 Gy, and 35 Gy of CSI, respectively [28]. Hence, the radiotherapy and the dose of irradiation are among the principal risk factors for an impaired intellectual outcome; actually, different studies underline a decrease in the dose of neuraxis' irradiation as an important strategy to reduce the incidence of long term neurocognitive deficits. Two independent studies, with 22 and 36 children, respectively, have clearly shown the benefit on cognition of lowering the CSI from 35 to 25 Gy in children with medulloblastoma [18, 27].

Lowering the CSI by 10 Gy increased the mean full-scale IQ of 10 points. Consequently, it is now widely accepted to treat standard-risk medulloblastoma (defined as little or no gross evidence of tumor as shown by postoperative MRI and

absence of metastatic disease with reduced irradiation despite the slightly higher trend for relapse observed in randomized trials.

2.1.5. Very Young Children

Are more vulnerable to the effects of the tumor, surgery radiotherapy, and chemotherapy [39 - 43]. Therefore, the impact of the patient's age at treatment and the level of radiation dose exposure on cognitive performance has been the focus of examination in several studies. Jannoun and Bloom [44] provided neurocognitive follow-up 3–20 years following irradiation in 62 children with a variety of brain tumors. The patient's age at the time of treatment was the most powerful determinant of ultimate IQ with those younger than 5 years at diagnosis being at greater risk (mean IQ=72), those of 6–11 years were at intermediate risk (mean IQ=93) and those older than 11 years functioning solidly in the normal range (mean IQ=107). Although not statistically significant, children presenting with hydrocephalus had a 10-point decrement in IQ compared to those with normal pressure.

A retrospective study of the Pediatric Oncology Group about average-risk (AR) patients randomly assigned to different therapeutic groups found that patients who received reduced dose CSI (23.4 Gy) and patients older than 8.8 years at the time of treatment presented higher cognitive functioning than patients who received standard-dose CSI (36 Gy) and patients who were younger at time of treatment [11]. Anyway, in a subsequent prospective study, even the AR patients treated with a reduced-dose CSI (23.4 Gy) and adjuvant chemotherapy experienced a reduction of 4.3 IQ points/yr over 3 years from treatment [16]. Palmer *et al.*, in a longitudinal design, reported in a group of 44 children a mean decline of 2.6 IQ points/yr following treatment with CSI (24.3 to 39.6 Gy) [45]. Patients older than 8 years of age and patients irradiated with a dose of CSI <35.2 Gy demonstrated higher cognitive functioning in comparison to patients younger or submitted to higher CSI doses. Moreover, they reported, in 50 patients treated with conventional-dose (35 to 40 Gy) CSI, the patterns of change in intellectual function over a period of 7 years from the diagnosis: the reduction in IQ was 2.2 points/yr [45].

Differently from younger patients, in whom the decline in IQ was more immediate, a late reduction in IQ was evidenced in patients treated at an older age. Collectively, these studies suggest that survivors who have received radiation therapy experience greater intellectual deficits than those who were not treated with radiation therapy, in particular at a younger age.

2.1.6. Sex

Some studies have hypothesized that females are at higher risk for cognitive deficits due to radiotherapy. Panwala *et al.* reported that female survivors were more affected when compared to males in terms of the living skills domain of adaptive functioning as well as of processing speed. Those deficits can negatively impact on daily living skills [46].

2.2. Pathophysiology of Late CNS Damage

It is asserted that the number of neurons cannot be expended after the 6th month of fetal life. During the first 3 years of life and to some extent up to 6 years, cerebral development includes cellular and axonal hypertrophy combined with a multiplication of dendrites and interneuronal connections [47].

The development of myelin normally continues after birth until the first 30 years of life and, while the cerebral hemispheres are about 50% myelin, patterns of myelination differ across brain regions [48]. The brain stem and cerebellar areas myelinate first, followed by the cerebral hemispheres and, finally, the anterior portions of the frontal lobes. Myelination of brain regions appears to parallel their functional maturation [49]. The inter-relatedness of cognitive functions and the brain regions that support these functions are reflected in the rich connections between myelinated axons in different brain areas.

Demyelination represents the most striking microscopic alteration following radiation and is responsible for white-matter necrosis. Pathogenesis is still unclear. It could be related to alterations of the microvasculature (affecting the endothelial cells), or of the oligodendrocytes that produce myelin.

Radiotherapy produces damage through the reduction of brain stem/precursor cells, located in the subgranular zone of the hippocampus dentate gyrus (with vascular damage or astrocytes activation) or in the subventricular zone of the anterior lateral ventricles [50, 51].

It is important to underline that all early manifestations of radiation related-damage determine long-term structural harm and consequent permanent cognitive impairment.

Among the alterations, there are oligodendrocytes or microvessels damage, loss of white matter wholeness, inflammation, and loss of cellular physiology. All these events lead to cognitive impairment, which, after 6 months, can be considered definitive. The dose at which radiation produces cognitive impairment is lower than that at which there is radionecrosis [52].

Two major clinical syndromes have been described following radiation, both in children and in adults:

(1). Cerebral radionecrosis whose risk has been estimated to 5% at 55 Gy fractionated, 15% at 60 Gy, and 20% at 65 Gy [53].

(2). Necrotizing leukoencephalopathy and mineralizing micro-angiopathy. The clinical course of leukoencephalopathy is gradual, characterized by decreased alertness and, eventually, the intellectual decline [54 - 56]. Neuropathologically, multiple necrotic lesions in the white matter near the ventricular characterize leukoencephalopathy. In mineralizing microangiopathy, neocalcifications are also detectable, especially in the basal ganglia. Several studies have identified the entity of the toxicity on white matter and evaluated the relationship between neurotoxicity and cognitive impairments related to childhood brain tumors.

It has been evidenced, comparing patients treated for medulloblastoma with age-matched controls with low-grade tumors of the posterior fossa treated only with surgery, that survivors of medulloblastoma presented a significantly smaller volume of cerebral white matter, an equal volume of grey

matter, and a greater volume of cerebrospinal fluid [57]. As expected, patients who survived medulloblastoma presented very low IQ scores, and this evidence is statistically correlated with volumes of cerebral white matter loss [10].

Subsequently, in patients treated for medulloblastoma, a longitudinal study demonstrated a significant decrease in the volume of cerebral white matter, which was quicker in patients who underwent 36 Gy CSI than in the group who underwent 23.4 Gy CSI [58]. Hence, a lesion in the white matter (both primary lesion site and the secondary result of radiation) interrupts or damages the complex information transmission network connecting the various brain areas, damaging the online consistency and speed of functioning of the system as a whole [20, 54].

Moreover, dose de-escalation demonstrates good outcomes, transferring less radiation to the brain, and consequently reducing cognitive impairment. Anyway, this evidence is not always valid.

The posterior fossa boost volume can also affect other structures located outside the area of interest, such as temporal lobes, cochlea, and parotid glands, compared to a boost limited to the tumor bed (TB).

Moxon-Emre *et al.* highlighted how patients with medulloblastoma treated with reduced-dose of craniospinal irradiation (CSR) and TB boost, experienced stable intelligence beyond their initial impairment and not worse survival. In contrast, patients treated with reduced-dose CSR and posterior fossa (PF) boost, standard-dose CSR and PF boost, standard-dose, and TB boost showed the same worse result. Therefore, limiting the boost volume to TB is important to reduce cognitive impairment [59, 60].

About chemotherapy, Gibson *et al.* analyzed methotrexato-related cognitive impairment.

This drug leads to activation of microglial, consequent astrocytes' reactivity, which brings about the disruption of oligodendrocytes and all these events lead to cognitive impairment [51, 61].

In particular, oligodendrocytes damage causes white matter damage and chemotherapy-cognitive impairment. Moreover, chemotherapy determines a syndrome of neurological dysfunction, defined "chemotherapy-related cognitive impairment (CRCI)" or "chemobrain", which is characterized by altered cognitive and executive functions, in particular: change in memory, attention, information processing, and capacity of organization [51, 61].

Recently, new drug treatments (such as nerve growth factor) and combined chemo-radiotherapeutic approaches have enabled to decrease doses of chemotherapy and/or CSI with a lower incidence of neurocognitive sequelae [61 - 63]. Moreover, new techniques of conformal radiation, which permit precise delivery of radiotherapy with reduction of damage to the surrounding brain tissue, have been introduced. In order to enhance the therapeutic window between efficacy and toxicity, RT has undergone revolutionary changes in recent years such as the development of intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT),

and proton beam radiation therapy (PBRT). These new technologic advances have allowed a modification of the type of radiation used as well as the shape and intensity of a given beam. These improvements participate in the enhancement of dose coverage of the tumor and sparing of normal tissues relative to traditional methods such as three-dimensional conformal radiation therapy (3DCRT). Results from recent trials are encouraging for the absence of significant adverse neurocognitive effects in preliminary data [64 - 66].

CONCLUSION

Neurosurgeons, pediatric oncologists, and radiotherapists have been successful in improving cure rates for most types of childhood brain tumors, including those of the posterior fossa. Nevertheless, the risks of neurocognitive impairment remain substantial, especially among individuals who were treated aggressively and at a young age. It is fundamental that, in the future, research should incorporate regular neuropsychological testing, new treatment modalities, neuroimaging, and longitudinal designs to minimize long-term complications and to develop new interventions to prevent the long-term neurotoxic effects experienced by children.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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