

Neurocognitive Outcomes in Pediatric Brain Tumors Survivors

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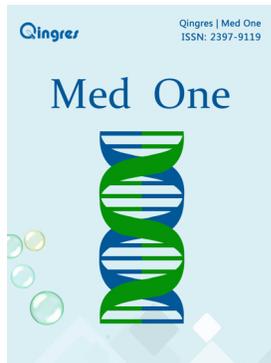
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ABSTRACT

Neurocognitive disorders are a common long-term effect in brain tumor survivors. The rate of intelligence quotient (IQ) decline is associated with a several risk factors, including tumor location, younger age at time of treatment, treatment intensity, in particular use of radiotherapy and radiotherapy dose, as well as clinical variables such as hydrocephalus and presence of epilepsy. Demyelination represents the most important alteration following radiation: loss of cerebral white matter is related to IQ decline, due to damage of the complex information transmission network connecting the various brain areas.

Recently, combined chemo-radiotherapeutic approaches and new technologies in radiation therapy have enabled to lower the frequency of neurocognitive deficits and improve the quality of life of paediatric brain tumours survivors.

Keywords: Neurocognitive impairment; Children; Brain tumor; Cancer survivor



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1 INTRODUCTION

Tumours of the central nervous system (CNS) are the most common form of solid tumours in childhood, accounting for 20 % of all pediatric malignancies^[1, 2]. Embryonal tumours and low-grade gliomas are the most common brain tumors in children, followed by high-grade glioma, brainstem glioma and ependymoma^[3]. There are two peaks in the incidence of brain tumours in children and adolescents. The first peak occurs the first decade of life a second much larger peak occurs in late adolescence and early adulthood.

Most children who have survived brain tumours have required surgery and focal or craniospinal irradiation (CSI), with or without systemic chemotherapy^[4-7]. The improvement in the effective therapy of childhood CNS tumors has resulted in a substantial increase in cure

rate and survival. However, neurocognitive disorders and sometimes severe disabilities have been documented in 40–100 % of long-term survivors^[8-10].

2 PRINCIPAL RISK FACTORS FOR COGNITIVE IMPAIRMENT

Neurocognitive late effects in childhood brain tumor survivors are relatively common and can be highly debilitating.

Intelligence quotient (IQ) measure, with a normative mean score of 100, is the most common method used to evaluate neurocognitive deficits.

A decline in IQ has been frequently associated with a decline in areas of attention, working memory, academic achievement and language^[11-13]. Moreover, several studies report difficulties in perception and estimation of time, fine motor coordination, visual motor and visual spatial skills in pediatric brain tumor survivors^[14-18].

The severity of intellectual outcomes of children with brain tumours depend on different factors. The influence of tumors at diagnosis has recently been studied in adults, whereas only few articles have evaluated the neuropsychological deficits in children before treatment^[19].

The tumour location is an important factor that causes selective site-dependent deficits. Infratentorial tumours are associated with a more limited cognitive decline than supratentorial tumours, even when radiotherapy is not used^[19]. In particular, Iuvone L. *et al* showed that all children with mental retardation at diagnosis had cortical tumors involving the mesial regions of the temporal lobes. Left hemispheric lesions are more likely to be associated with verbal deficits, whereas right hemispheric lesions are associated with visual perceptual deficits^[20]. Moreover, hemispheric tumours result in lower IQ than tumours of the third or fourth ventricle, although children with fourth ventricle tumours show significant declines in their IQ over time.

Tumor volume is a less crucial factor than site for cognitive deficits. Small tumors in critical areas may have a greater impact on neurocognitive outcome than some large tumors.

Symptom duration and the presence of epilepsy are the main clinical factors affecting cognitive status at diagnosis^[19]. In epileptic children neurocognitive outcome is markedly impaired and declines with time. In particular, in children with grade III epileptic syndromes receiving several antiepileptic drugs maximum cognitive impairment was found, as the

result of seizures and pharmacological agents^[21].

Obstructive hydrocephalus also plays a role in neurocognitive outcomes in pediatric brain tumor survivors. The level of intracranial pressure and, above all, the duration of the pressure on the fibres of the white matter, mainly of the frontal lobes, are the main factors causing mental deterioration in children with hydrocephalus^[22-24].

Despite the use of computer-guided neurosurgical techniques, surgical resection may add further damage to those already existing, due to prolonged retraction of the frontal lobes to reach tumours located elsewhere. Moreover in patients with posterior fossa tumours the incision or destruction of the cerebellar vermis causes complex alterations in social and communicative behaviour^[25-27].

Only a small percentage of children affected by brain tumor can be cured by surgery alone. Post-surgical treatment, including chemotherapy and radiotherapy (RT), is based on the histology, presence of metastatic lesions at diagnosis and extent of resection. The potentially devastating effects of RT on growing individuals are well known. Several studies have demonstrated marked losses of IQ of up to 30 points or more which are most predominant in young children, particularly those less than seven or eight years of age^[28]. In one study of 56 pediatric brain tumor survivors in whom 22 received radiation therapy, IQ scores were less than 90 in 68 % of survivors treated with RT, compared with 18 % of non-irradiated patients^[28]. Hirsch *et al* compared a series of children irradiated for a medulloblastoma with a series of children with cerebellar astrocytoma treated with surgery alone^[22]. Global IQ exceeded 90 in 2 and 62 %, school performance was altered in 75 and 27 %, and behaviour was compromised in 93 and 59 % respectively. Moreover, Grill *et al* analysed 31 children with posterior fossa tumours treated with RT and off therapy for at least 1 year. Patients were divided into 3 groups according to the CSI doses. Neurocognitive deficits occurred in most of the patients, even after posterior fossa irradiation only. Full-scale IQ score was related to CSI dose and was 84.5, 76.9, and 63.7 for 0 Gy, 25 Gy, and 35 Gy of CSI, respectively^[29]. Two independent studies, with 22 and 36 children respectively, have shown the benefit on cognition of lowering the CSI from 35 to 25 Gy in children with medulloblastoma^[22, 30]. This has been the rationale to decrease the craniospinal dose from 36 to 23.4 Gy in standard risk medulloblastoma, establishing better cognitive outcome after craniospinal dose reduction^[31].

However, despite reductions in CSI dosing and efforts to limit the boost volume, the age of the

patient at treatment remains the most important risk factor for neurocognitive deficits among survivors of brain tumors^[31]. Very young children are more vulnerable to the effects of the RT and intellectual deficits are greater in survivors who are treated with RT at a younger age than older patients^[32, 33]. A retrospective study on 62 children with different brain tumours described neurocognitive outcome 3–20 years following irradiation^[34]. The most serious neurocognitive deficits were identified in children younger than 5 years at diagnosis. IQ was in the normal range in patients older than 11 year, whereas patients aged 6–11 years were stratified into intermediate risk.

Moreover, Mulhern *et al.* performed a retrospective study on average-risk (AR) patients with medulloblastoma and found that patients receiving standard-dose CSI (36 Gy) and patients younger at time of treatment showed lower IQ than patients receiving reduced dose CSI (23.4 Gy) and aged > 8.8 years^[13]. However, in a subsequent prospective study, even the AR patients who had received reduced-dose CSI presented a decline of 4.3 IQ points per year over a 3-year period from treatment^[17].

3 PATHOPHYSIOLOGY OF LATE CNS DAMAGE

During the first 6 years of life, cerebral development is characterized by cellular and axonal hypertrophy, multiplication of dendrites, interneuronal connections and development of myelin that continues after birth into the third decade of life^[35,36]. Patterns of myelination differ across brain regions: the brain stem and cerebellar areas myelinate first, followed by the cerebral hemispheres and the anterior portions of the frontal lobes. The connections between myelinated axons in different brain areas support the cognitive functions^[37].

Cerebral irradiation is responsible of neurotoxicity and cognitive deficits in childhood brain tumor survivors, by white-matter necrosis and demyelination. Several studies have evaluated toxic effects of RT on white matter and damage of the information transmission network connecting the various brain areas.

Pathogenesis is still unclear. It could be related to alterations of the endothelial cells or of the oligodendrocytes that produce myelin. In children and in adults underwent RT cerebral radionecrosis has been reported. The risk has been estimated to 5 % at 55 Gy fractionated, 15 % at 60 Gy, and 20 % at 65 Gy^[38].

Moreover necrotizing leukoencephalopathy and mineralizing micro-angiopathy have been described^[39, 40], characterized by a gradual decreased alertness and intellectual decline^[41]. Neuropathologically, necrotic lesions in the periventricular white matter have been reported and neocalcifications, especially in the basal ganglia, have been identified in mineralizing microangiopathy.

Reddick *et al* compared children irradiated for a medulloblastoma with a series of children with low grade tumours of the posterior fossa who had received surgery alone. Survivors of medulloblastoma had a significantly smaller volume of cerebral white matter, a greater volume of cerebrospinal fluid, and an equal volume of grey matter^[42]. As expected, IQ scores were significantly lower in survivors of medulloblastoma, associated with volumes of cerebral white matter^[12]. Subsequently, Reddick *et al.* showed that decrease in the volume of cerebral white matter in patients with medulloblastoma underwent CSI was more rapid in patients receiving 36 Gy than in patients receiving 23.4 Gy craniospinal irradiation^[43].

4 CONCLUSIONS

Neurosurgeons, paediatric oncologists, and radiation oncologists have been successful in improving cure rates for most types of childhood brain tumours. Nevertheless, the risks of neurocognitive impairment remain substantial. Tumor location, symptom duration, presence of epilepsy, dose of RT, volume of the brain that receives treatment and age of the patient at treatment are the major determinants of cognitive performance. To date, RT remains a key modality in the curative treatment approach of patients with brain tumors. To reduce neurocognitive morbidity, new protocols have been designed to limit radiation dose using risk-adapted irradiation dosing. Moreover, new techniques of conformal radiation have been introduced in order to enable precise delivery of RT with less damage to the surrounding brain tissue.

In children with brain tumors a neuropsychological surveillance should be routine in order to optimize their outcomes, by a early and preemptive intervention.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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