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Executive function deficits in pediatric cerebellar tumor survivors

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ABSTRACT

Background and aims: Besides motor function the cerebellum subserves frontal lobe functions. Thus, we investigated executive functions in pediatric posterior fossa tumor survivors.

Methods: We tested information processing, aspects of attention, planning and intelligence in 42 pediatric posterior fossa tumor survivors (mean age 14.63 yrs, SD 5.03). Seventeen low-grade tumor patients (LGCT) were treated with surgery only and 25 high-grade tumors patients (HGCT) received postsurgical adjuvant treatment. We evaluated simple reaction time, executive functioning, i.e. visuospatial memory, inhibition, and mental flexibility using the Amsterdam Neuropsychological Tasks program, whereas forward thinking was assessed with the Tower of London-test. Intelligence was determined using the Wechsler Intelligence Scale. Ataxia was assessed with the International Cooperative Ataxia Rating Scale.

Results: About one third of each patient group showed forward thinking scores below one standard deviation of the norm. Impaired forward thinking correlated significantly with degree of ataxia ($r = -0.39$, $p = 0.03$) but not with fluid intelligence. Both patient groups exhibited executive function deficits in accuracy and reaction speed in more difficult tasks involving information speed and attention flexibility. Still, HGCT patients were significantly slower and committed more errors. Working memory was inferior in HGCT patients.

Conclusion: Pediatric cerebellar tumor survivors with different disease and treatment related brain damage exhibit similar patterns of impairment in executive functioning, concerning forward thinking, inhibition and mental flexibility. The deficits are larger in

Abbreviations: CB, cerebellum; PFC, prefrontal cortex; MB, medulloblastoma; PA, pilocytic astrocytoma; EP, ependymoma; HGCT, high grade cerebellar tumor; LGCT, low grade cerebellar tumor; ToL, Tower of London test; ToL-t, initial thinking time, preplanning time; ToL-percentile, percentile rank of solved problems; ToL-intermissions, number of pauses after the initial touch of the ball; ANT, Amsterdam Neuropsychological Task program; BS, baseline speed; FI, feature identification; SSV, shifting attentional set; ICARS, international cooperative ataxia rating scale; HAWIK-III, 3rd edition of the German Hamburg–Wechsler intelligence test for children; HAWIE, Hamburg–Wechsler intelligence test for adults; FSIQ, full scale IQ; VIQ, verbal IQ; PIQ, performance IQ; K-ABC, Kaufman assessment battery for children; RT, reaction time; WCST, Wisconsin card sorting test; WM, working memory; FA, fractional anisotropy.

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high-grade tumor patients. The pattern of function loss seen in both groups is most probably due to comparable lesions to cerebro-cerebellar circuits that are known to modulate critical executive functions.

1. Introduction

Almost half of all pediatric brain tumors arise in the posterior fossa.[1] The most common cerebellar low-grade tumor, pilocytic astrocytoma (PA), is treated with surgical resection only. In contrast high-grade medulloblastoma (MB) patients further require craniospinal irradiation, a local boost and chemotherapy.[2] Treatment of infratentorial ependymomas (EP) consists in resection followed by local irradiation in case of WHO grade II or III histology.[3]

In view of improved survival rates, long-term cognitive, behavioral, and affective sequelae have received considerable interest in cerebellar tumor survivors.[4,5] Poor intellectual outcome has been consistently documented in MB patients. Especially in the acquisition of new skills and knowledge MB survivors lag behind healthy peers.[6] This dysfunction is considered to be due to inferior working memory, attention and processing speed.[6–8] The deficits of higher mental function in MB patients have been primarily attributed to the neurotoxic effect of craniospinal irradiation and secondly to the interplay with chemotherapy.[9,10] In children with cerebellar PA intelligence seems to be generally spared with the exception of inferior verbal intelligence.[11] Impairments of attention, parts of executive function, and information processing speed were also reported in PA survivors.[5,11–13] Planning abilities were previously investigated using multiple function tests that cover a broad spectrum of executive functions, such as the Wisconsin Card Sorting Test (WCST).[8,11,14] These studies have reported discordant findings concerning planning abilities of pediatric cerebellar tumor survivors, with PA survivors performing within versus below the norm variation. Imaging, neuropsychological and animal studies[15,16] strengthen the role of the cerebellum (CB) as a modulator of prefrontal cortex (PFC) functions. The PFC is dedicated to temporal integration and planning of behavior and actions, inhibitory control of responses, regulation of emotions, direction of attention, and working memory.[17,18] Reciprocal neural loops connecting the CB with the PFC are the underpinnings of this regulatory system.[4,19] Myelination of these white matter pathways proceeds from childhood to adolescence.[20] In parallel, maturation of different cognitive abilities follows a stepwise process. Planning, processing speed, goal setting and cognitive flexibility are thought to evolve until mid-adolescence whereas attention, self-regulation and inhibition mechanisms develop rapidly in early childhood.[21,22] Thus, lesions to the developing cerebro-cerebellar neural network orchestrating higher mental functions by cerebellar tumor disease and its treatment render patients highly vulnerable for suffering from deficits of these functions.[23]

The present study focused on profiling executive functioning of children and adolescents that suffered from low- or high-grade cerebellar tumors and were exposed to different treatment associated neurotoxic effects. In this setting we tested certain aspects of the theorized executive function system such as planning (formulation, evaluation and selection of a sequence of representation of information and executive actions to achieve a desired goal), working memory (maintaining as well as manipulation/monitoring of representation of information in its absence and the control of activation of these representations, here visuospatial information), inhibition of prepotent responses (i.e. responses with immediate reinforcement available or previously associated) and task flexibility (switching between or continuous monitoring of diverse stimulus–response associations (attentional sets)).[24] We sought to distinguish quality and quantity of cognitive deficits caused by confined local damage to the cerebellar structures (present in the low-grade tumor group) from the aggravating effects of the global impact of adjuvant treatment (additionally present in the high-grade tumor group). To this purpose, in addition to the clinical assessment of ataxia applying the International cooperative ataxia rating scale (ICARS) we used a battery of neurocognitive assessments, i.e. the Hamburg Wechsler Intelligence Test (HAWIK/HAWIE), the Amsterdam Neuropsychological Tasks (ANT) program[25] and the Tower of London (ToL).[26] In contrast to multiple function tests, the ANT program allows to precisely evaluate speed and accuracy of specific aspects of executive function, such as working memory processes, cognitive flexibility and inhibition. This is the first study using this approach in pediatric cerebellar tumor survivors. We hypothesized that both patient groups would perform worse when compared to healthy peers due to loss of cerebellar function. In addition, children who received adjuvant treatment were predicted to exhibit greater deficits of executive function when compared to those treated with resection only due to irradiation and chemotherapy associated neurotoxicity.

2. Material and methods

42 children and adolescents diagnosed with a posterior fossa tumor were recruited at the Department of Pediatric Oncology and Hematology of Charité-Universitätsmedizin Berlin. All subjects and their parents gave written informed consent. The institutional ethics committee approved the study.

16 patients had a PA, 23 were diagnosed with a MB and three suffered from an EP. Patients were allocated to two groups: a low-grade cerebellar tumor cohort (LGCT), i.e. sixteen PA and one EP patients and a high-grade cerebellar tumor group (HGCT) comprising 23 MB and two EP patients