Cognitive changes related to infratentorial brain neoplasms in pediatric patients

Mudanças cognitivas relacionadas a neoplasias cerebrais infratentoriais em pacientes pediátricos

DOI:10.34119/bjhrv4n3-318

Recebimento dos originais: 04/02/2021
Aceitação para publicação: 01/03/2021

Letícia Pimentel Duarte
Discente de Psicologia
Faculdade Pernambucana de Saúde
Endereço completo: Avenida Pedro Paes Mendonça, 200 - Boa Viagem - Recife - PE, 51.020-480
E-mail: leticiap.duarte@gmail.com

Camilla de Andrade Tenorio Cavalcanti
Mestrado em Biociência Animal
Universidade Federal Rural de Pernambuco
Endereço completo: Rua Dom Manuel de Medeiros, s/n - Dois Irmãos, Recife - PE, 52171-900
E-mail**:** camillat.nutricionista@gmail.com

Isvânia Maria Serafim da Silva Lopes
Doutorado em Tecnologias Energéticas e Nucleares
Departamento de Biofísica e Radiobiologia da Universidade Federal de Pernambuco
Endereço completo: Av. Prof. Moraes Rego, 1235 - Cidade Universitária, Recife - PE - CEP: 50670-901
E-mail: isvania@gmail.com

ABSTRACT

Cancer is a set of numerous diseases characterized by the abundant and disordered growth of cells. In the pediatric population, central nervous system tumors account for 20% of neoplasms. In this scenario, it is necessary to highlight that patients with tumors in the posterior fossa and aggressive treatments, such as exposure to cranial radiotherapy, have been associated with a decline in cognitive functioning. Thus, the main objective of this research was to evaluate, through theoretical and empirical studies of national and international literature, the cognitive impact on individuals with brain neoplasms in the posterior fossa region. To achieve this goal, the descriptors "brain neoplasms", "cognitive dysfunction" and "child development" were used in the LILACS-BVS, SciELO, and MEDLINE/PubMed databases, being considered as inclusion criteria articles published in the last five years (2016 -2020) and excluding articles whose methodology was inconsistent and bibliographic reviews; 4 articles were selected as a research sample. Based on the selected articles, it can be identified, in general, that the association between cognitive decline and infratentorial brain neoplasms is due to the form of treatment normally suggested to deal with this disease. Furthermore, a direct relationship was perceived between aggressive treatments – such as chemotherapy and radiotherapy – and

long-term decline. However, few articles on the subject were identified, and it is possible to conclude that there is a gap in this segment, making it necessary to develop more research in the area.

Keywords: brain neoplasms, pediatrics, cognition, child development.

RESUMO
O câncer é um conjunto de inúmeras doenças que tem como característica comum o crescimento abundante e desordenado de células, sendo que na população pediátrica os tumores do sistema nervoso central (SNC) correspondem a 20% das neoplasias. Nesse cenário, é necessário destacar que pacientes com tumores na fossa posterior e tratamentos agressivos, como a exposição à radioterapia craniana, tem sido associado ao declínio no funcionamento cognitivo. Assim, objetivo central da presente pesquisa foi avaliar, através de estudos teóricos e empíricos da literatura nacional e internacional, o impacto cognitivo em indivíduos com neoplasias encefálicas na região da fossa posterior. Para atingir esse objetivo foram utilizados os descritores *"brain neoplasms"*, *"cognitive dysfunction"* e *"child development"* nas bases de dados LILACS-BVS, SciELO e MEDLINE/PubMed, sendo considerado como critério de inclusão artigos publicados nos últimos cinco anos (2016-2020) e de exclusão artigos cuja metodologia fosse inconsistente e revisões bibliográficas; desse modo, foram selecionados 4 artigos como amostra da pesquisa. Com base nos artigos selecionados, pode-se identificar, de modo geral, que a associação entre declínios cognitivos e neoplasias encefálicas infratentorial se dá devido a forma de tratamento, normalmente sugerida para enfrentar esta doença. Ademais, foi percebida uma relação direta entre os tratamentos agressivos – como quimioterapia e radioterapia – e o declínio a longo prazo. No entanto, foram identificados poucos artigos sobre a temática, sendo possível concluir que existe uma lacuna nesse segmento, tornando necessário o desenvolvimento de mais pesquisas na área.

Palavras-chave: neoplasias cerebrais, pediatria, cognição, desenvolvimento infantil

1 INTRODUCTION

Cancer is a set of numerous diseases that have as a common characteristic the abundant and disordered growth of invading cells from tissues and organs, as well as having histopathological and clinical behavior similarities (LITTLE, 1999). Currently, in Brazil and developed countries, 8% of the total deaths in children and youths (between 0 and 19 years old) are due to cancer, leading to the cause of death from disease in this age group. In 2020, according to a survey by the *Instituto Nacional do Câncer* (INCA), it is estimated the emergence of 8,460 new cases in children and adolescents, among which 4,310 are males and 4,150 are females.

In the pediatric population, central nervous system (CNS) tumors account for 20% of neoplasms, being the second most frequent, affecting mostly children under 15 years of age (INCA, 2016; INCA, 2018). These tumors have specific characteristics and, in the

first decade of the patient's life, they are mostly developed in the infratentorial region (or region of the posterior fossa) which corresponds to the region below the tent of the cerebellum; or in the cerebellar tentorium, dura mater membrane that covers the cerebellum and supports the occipital lobes (FURRER e SUZUKI, 2003; ROOSTAEI *et al.*, 2014; INCA, 2018). Among the most frequent types of tumors in the pediatric posterior fossa, medulloblastomas and pilocytic astrocytomas stand out (SPENNATO *et al.*, 2015).

Medulloblastoma is a tumor originating predominantly in the cerebellar vermis and can be considered strongly malignant, is characterized by a high degree of cellularity and mitotic potential, also having a great infiltration potential and a strong disposition to dissemination through the CSF and neuro- axis, which may result in worse prognoses (RIES *et al.*, 1999). Pilocytic astrocytoma, on the other hand, is the most frequent of the cerebellar astrocytomas, being relatively uncommon in the first year of life; despite this, they have an average of onset between the first 18 months of age and are generally associated with some syndrome, including Type I Neurofibromatosis, Turcot Syndrome, PHACE Syndrome and Ollier's disease (SPENNATO *et al.*, 2015).

In the 60s, children and adolescents affected by cancer had a low prognosis, and, because of that, a greater focus was attributed to medical interventions to lower the mortality rate, neglecting over the decades the possible sequelae in survivors. However, the advancement of technology in these treatments - surgery, radiotherapy, and chemotherapy - has significantly increased the survival rate (DUFFNER, 2010), awakening the need to assess the quality of life of those who survived brain tumors.

Bloom *et al.* (1969) were pioneers in recognizing and highlighting in the literature the true risk presented by brain tumors and their treatments for the well-being of patients. From these findings, the professional team then has dedicated attention to this topic due to the greater focus on medical interventions to lower the mortality rate. Assignable to the significant increase in the survival rate of patients, Spennato *et al.* (2015) highlight the association between aggressive treatments and high neurotoxicity, causing a neuropsychological impairment for the patient, with an emphasis on a decline in executive functions.

Executive functions (EF) encompass several cognitive skills needed for the regulation of behavior and emotions (KRIVITZKY *et al.*, 2016), being referred to mental processes at a complex level, which arrange purposeful, goal-directed activities. These functions are fundamental and allow the modification of action, inhibition of

inappropriate activities, and orientation of behavior according to social rules, internal goals, and personal intentions (JURADO e ROSSELLI, 2007). It is also necessary to emphasize that the decline in cognitive functioning of recovered patients has been associated with cerebellar dysfunction, caused mainly in cases of surgical resection of tumors in the posterior fossa and aggressive treatments such as exposure to cranial radiotherapy (MULHERN *et al.*, 2004).

Therefore, due to the risks to EF presented by brain tumors, especially when located in the posterior fossa region – more common among children and adolescents, the present review aimed to evaluate, through theoretical and empirical studies in the national and international literature, such as cognitive impact in individuals with brain neoplasms in the posterior fossa region.

2 MATERIAL AND METHODS

The present study is a literature review in the integrative category, whose search was guided by the questioning of what is the relationship between cognitive decline and infratentorial brain neoplasms. To answer it, the following descriptors were used: “brain neoplasms”, “cognitive dysfunction” and “child development”, duly verified on the *Descritores em Ciências da Saúde* (DECS-BVS) platform.

These descriptors were applied to the *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS-BVS), Scientific Electronic Library Online (SciELO) e Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed) databases, connected by the Boolean operator “AND”, and occurred between January and April 2020, resulting in only articles in PubMed (n = 7).

The inclusion criteria were articles whose main objective was aligned with the question about the relationship between cognitive decline and infratentorial brain neoplasms, published in the last five years (2016-2020). Exclusion criteria were applied to articles whose methodology was inconsistent and literature reviews.

At first, when applying the platform's filter: articles published in the last five years (2016 - 2020), 6 articles related to the proposed theme were found. From a critical reading of the abstracts, an article that did not fit the initial objective of the study and an article that, even after applying the filter, was published in 2015 were excluded. Thus, 4 articles that met the objectives and inclusion criteria of the present study were selected.

3 RESULTS AND DISCUSSION

In Table 1, it is possible to identify the main information of each study, in which it is noteworthy that the collection of data from the articles occurred, mostly, in a single country: the United States; apart from the most recent. Within the 5 years, established as an inclusion criterion, publications are restricted to the first 3 years (2016; 2017; 2018), creating a scientific gap in this field of study in recent years.

Table 1. Results of the articles found using the descriptors: "brain neoplasms", "cognitive dysfunction" and "child development". Source: Research Archives.

AUTHOR/YEAR	TITLE	COUNTRY
Krivitzky *et al.*, 2016	Executive Functioning Profiles from the BRIEF across Pediatric Medical Disorders: Age and Diagnosis Factors.	United States
McCurdy *et al.*, 2016	Discrepancies among Measures of Executive Functioning in a Subsample of Young Adult Survivors of Childhood Brain Tumor: Associations with Treatment Intensity.	United States
Araujo *et al.*, 2017	Profile of Executive Function Across Children with Distinct Brain Disorders: Traumatic Brain Injury, Stroke, and Brain Tumor	United States
Sekers *et al.*, 2018	Impaired Recent, but Preserved Remote, Autobiographical Memory in Pediatric Brain Tumor Patients.	Canada

Beforehand, it is necessary to emphasize that a standard for screening these deficits was not established in different studies, generating a variety of clinical findings in the scientific literature, and making it difficult to compare the results. Thus, the next topics bring the methods used in these surveys and their respective results.

3.1 METHODS APPLIED IN THE ANALYZED STUDIES

In 2016, Krivtzky and colleagues conducted a retrospective cross-sectional study of 734 children aged 5-18 years and applied the Behavior Rating Inventory of Executive Functioning (BRIEF) to compare the EF of different clinical conditions in pediatrics and explore the influence the age of diagnosis and its evolution. The sample was divided into 5 clinical diagnosis groups: brain tumor, acute lymphoid leukemia (ALL), epilepsy (EPI), neurofibromatosis type 1 (NF1), and ornithine transcarbamylase deficiency (OTC-D); in addition to attention deficit hyperactivity disorder (ADHD) control group and the healthy control group.

Likewise, other researchers have awakened interest in this same matter, however, on this occasion, opting to examine EF among brain dysfunctions children and the control group characterized by children without brain dysfunctions (ARAUJO et al., 2017). For

this purpose, 336 children were selected, diagnosed with the following pathologies: children with arterial ischemic cerebrovascular accident (n = 36; 6-16 years of age); traumatic brain injury (n = 82; 8-13 years of age); and brain tumor (n = 74; 9-18 years of age). Each group in the control sample corresponded to a group of children with brain injury: orthopedic injury (n = 61); asthma (n=15); classmates without medical injuries (n = 68).

When analyzing the participants, those with brain tumors, 43% (n = 32) had a brain tumor in the infratentorial region. The instruments selected for data collection were the Wechsler Abbreviated Scale of Intelligence (WASI), to estimate general intelligence ability; three subtests of the Test of Everyday Attention: Children's Version (TEA-Ch): Creature Counting, Walk-Don't-Walk, and Code Transmission to measure EF.

In a new perspective, aiming at an analysis of long-term effects, McCurdy *et al.* (2016) selected a sample of 34 participants (52.9% women) aged 18-30 years, childhood brain tumor survivors, and their respective mothers. The objective was to compare the results of the tests applied to the survivors, their respective mothers, and the performance of their associations, with the history of the intensity of the oncological treatment.

The instruments selected for data collection aimed to measure the participant's EF were: Trail Making Test and Tower Test of Delis-Kaplan Executive Function System (D-KEFS), Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A) Self Report (BRIEF-SR), and Informant Report (BRIEF-IR); working memory: Digit Span (DS) and Letter-Number Sequencing (LNS), Wechsler Adult Intelligence Scale (WAIS-IV) subtests; and treatment intensity: Intensity Treatment Rating Scale-3 (ITR-3) – modified and adapted for childhood brain tumor survivors.

In 2018, the researchers raised a new hypothesis, mismatching the focus of EF in general, and restricting the differences in the quality of autobiographical memory between patients who survived the posterior fossa tumor (PFT) in childhood and the control group. The sample consisted of 13 PFT survivors (n = 12 medulloblastoma; n = 1 ependymoma), who had been treated with surgical resection of the tumor, followed by chemotherapy and craniospinal radiotherapy for 1 year or more of their participation in the study and by the control group (SEKERS *et al.*, 2018).

As data collection instruments, the Children's Autobiographical Interview (CAI), the standardized memory test, and the MRI were used between 2013 and 2015. The healthy control participants had no history of traumatic brain injury, neurological

condition, learning disability, or developmental delay. All participants spoke English fluently and did not differ in maternal education, or terms of class assessment.

3.2 RESULTS OBTAINED IN THE ANALYZED STUDIES

Regarding cognitive decline associated with brain tumors, McCurdy *et al.* (2016) divided their sample of survivors of childhood brain tumors into groups according to the intensity of treatment: intensive/more intensive, moderate/medium, and minimal. When compared, the survivors of the intensive/more intensive group showed significantly lower performance in most of the objective measures of EF. Except for TWR-A, the intensive/more intensive group differed from the minimal group, but there was no discrepancy as to the moderate/medium group.

Moreover, in later research, it was observed that the performance of the clinical group with brain tumor did not vary according to the tumor area, or that those who were treated with surgical resection. However, those who underwent neurotoxicity through chemotherapy had an overall poorer performance on the TEA-Ch subtests. Those who were treated using radiotherapy performed less well than those who were not submitted to this therapy. Those who experienced only surgical resection performed better than those who went through any form of auxiliary treatment (ARAUJO *et al.*, 2017), making evident the relationship between cognitive decline and the aggressiveness of cancer treatment.

In 2018, an experiment was conducted with the clinical sample exclusively composed of patients diagnosed with PFT, who are more likely to undergo chemotherapy and radiotherapy treatments. The results obtained in the research show a decline in the autobiographical memory component, in relation to the control group (in recent moments, but not too remote memories). Patients with PFT also reported shorter memories compared to the control group. In relation to recent memories reported by the control group, patients with PFT report significantly less perception/sensitivity and details of place, indicating a tendency towards less perceptual details (SEKERS *et al*., 2018).

No differences in the quality of recent and remote non-episodic memories were reported. The findings highlight the increased dependence enclosed by time and the proportion of non-episodic memory recovered, although suggest that these, in patients along with PFT, contain non-episodic information comparable to the control group. This research also accessed findings of verbal disfluency in patients with PFT, confirming previous reports of language impairment (SEKERS et al., 2018).

Respecting brain changes, a reduction in hippocampal volume, fornix, and the cerebral precuneus region was detected in patients with PFT. No major changes were found in relation to the hemispheres, nor interaction of the hemispheric group, but a main effect of the clinical group was confirmed, suggesting that the treatment with radiotherapy bilaterally affected the structures of the medial temporal lobe. It was also analyzed whether the time of radiotherapy treatment may have affected the production of internal details, however, probably due to the low potency sample, a clear pattern in this relationship was not evident, generating a gap and the need for further development in this regard (SEKERS et al., 2018).

The association between the aggressiveness of cancer treatment and decline in EF was also questioned from the maternal viewpoint, compared with personal reports from survivors. The intensive/more intensive group had higher discrepancy scores than the other groups, and when questioned, survivors reported fewer executive problems compared to their mothers' reports. As to the minimum group, mothers reported a lower degree of difficulties in EF than survivors reported (MCCURDY *et al.*, 2016).

Hence, it can be concluded that survivors exposed to more intensive therapy perceive their EF skills more intact compared to maternal perception, while those with less intensive treatment rated their executive skills as being more compromised, concerning maternal responses (MCCURDY *et al.*, 2016). The discrepancy in the parents' perception about the level of impairment of the EF of cancer patients is also reported in the clinical findings of Krivtzky *et al.* (2016), who conclude that teachers are more likely to notice and report problems in EF than the parents themselves.

Considering the increase in life expectancy in cancer patients, it is essential to guide patients about possible cognitive changes, as well as strategies to reduce these damages. Health professionals need to be trained and prepared to identify these symptoms, since, in most cases, these sequelae are neglected. Among the studies analyzed, only the clinical findings by Krivtzky *et al.* (2016) raise the hypothesis that the clinical groups diagnosed with a brain tumor, and ALL do not differ, in terms of EF, from the control group. That is, they did not obtain significant changes that characterized their cognitive functioning as inferior to the control group.

4 CONCLUSION

The association between cognitive decline and infratentorial brain neoplasms is due to the form of treatment commonly suggested to face this disease. A direct

relationship was perceived between aggressive treatments – such as chemotherapy and radiotherapy – and long-term cognitive impairment. The wide range of applied cognitive assessments ends up making it difficult to compare the results obtained in research, and may even generate a distinction between the results, therefore, it becomes necessary to standardize these tests.

Concerning the survivor and their mothers, a distorted perception of the same issue was observed - the impairment of EF. Furthermore, the greater sensitivity of teachers to perceive this commitment was also perceived, requiring a deeper search to make sense of the role of the mother figure in this scenario.

Lastly, there is a literary gap, in which the most recent studies were published in 2018, headlining the urgency for further and new research on this topic. It is extremely necessary to analyze these cognitive declines to infratentorial brain neoplasms to stimulate a search for less aggressive drugs and toxic to the nervous system, as well as the need to implement neurocognitive therapies to minimize permanent damage to patients.

REFERENCES

ARAUJO, G. C.; ANTONINI, T. N.; ANDERSON, V.; VANNATTA, K. A.; SALLEY, C. G.; BIGLER, E. D. et al. Profiles of Executive Function Across Children with Distinct Brain Disorders: Traumatic Brain Injury, Stroke, and Brain Tumor. **Journal of the International Neuropsychological Society:** JINS, p. 529–538, 2017. doi:10.1017/S1355617717000364

BLOOM, H. J. G.; WALLACE, E. N. K.; & HENK, J. M. The treatment and prognosis of medulloblastoma in children. **American Journal of Roentgenology**, p. 43–62, 1969. doi:10.2214/ajr.105.1.43

DUFFNER, P. K. Risk factors for cognitive decline in children treated for brain tumors. **European Journal of Pediatric Neurology**, p. 106-115, 2010. doi:10.1016/j.ejpn.2009.10.005

FURRER, A. A.; SUZUKI, S. H. Meduloblastoma. In: Anamaria Arbo Furrer; Carlos Alberto Martinez Osório; Paulo Issamu Sanematsu Jr; Patrícia Imperatriz Rondinelli. (Org.). **Neurologia Oncológica Pediátrica.** São Paulo: Le mar, p. 295-304, 2003.

INCA. Coordenação de Prevenção e Vigilância. **Incidência, mortalidade e morbidade hospitalar por câncer em crianças, adolescentes e adultos jovens no Brasil:** informações dos registros de câncer e do sistema de mortalidade. Rio de Janeiro: Inca, 2016.

INCA. **Tumores do Sistema Nervoso Central.** Brasília, 16, Nov. 2018. Disponível em: <https://www.inca.gov.br/tipos-de-cancer/cancer-infantojuvenil/tumores-do-sistema-nervoso-central/profissional-de-saude>. Acesso em: 10, Jun. 2020.

JURADO, M. B.; & ROSSELLI, M. The Elusive Nature of Executive Functions: A Review of our Current Understanding. **Neuropsychology Review**, p. 213–233, 2007. doi:10.1007/s11065-007-9040-z

KRIVITZKY, L. S.; WALSH, K. S.; FISHER, E. L.; & BERL, M. M. Executive functioning profiles from the BRIEF across pediatric medical disorders: Age and diagnosis factors. **Child neuropsychology:** a journal on normal and abnormal development in childhood and adolescence, p. 870–888, 2016. doi: 10.1080/09297049.2015.1054272

LITTLE, J. Introduction. In: LITTLE, J. Epidemiology of childhood cancer. Lyon: **IARC**, p. 1-9, 1999.

MCCURDY, M. D.; TURNER, E. M.; BARAKAT, L. P.; HOBBIE, W. L.; DEATRICK, J. A. et al. Discrepancies among Measures of Executive Functioning in a Subsample of Young Adult Survivors of Childhood Brain Tumor: Associations with Treatment Intensity. ***Journal of the International Neuropsychological Society: JINS***, p. 900–910, 2016. doi:10.1017/S1355617716000771

MULHERN, R. K.; MERCHANT, T. E.; GAJJAR, A.; REDDICK, W. E.; & KUN, L. E. Late neurocognitive sequelae in survivors of brain tumours in childhood. **The Lancet Oncology**, p. 399–408, 2004. doi:10.1016/s1470-2045(04)01507-4

RIES, L. A. G.; SMITH M. A.; GURNEY, J.G.; LINET, M.; TAMRA, T. et al. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. **NIH Pub.** Bethesda, MD, 1999.

ROOSTAEI, T.; NAZERI, A.; SAHRAIAN, M. A.; & MINAGAR, A. The Human Cerebellum. **Neurologic Clinics**, p. 859-869, 2014. doi:10.1016/j.ncl.2014.07.013

SEKERES, M. J.; RIGGS, L.; DECKER, A.; MEDEIROS, C. B.; BACOPULOS, A. et al. Impaired Recent, but Preserved Remote, Autobiographical Memory in Pediatric Brain Tumor Patients. **Journal of Neuroscience**, p. 8251-8261, 2018. doi:10.1523/JNEUROSCI.1056-18.2018

SPENNATO, P.; NICOSIA, G.; QUAGLIETTA, L.; DONOFRIO, V.; et al. Posterior fossa tumors in infants and neonates. **Child's nervous system:** official journal of the International Society for Pediatric Neurosurgery, p. 1751–1772, 2015. doi:10.1007/s00381-015-2783-6