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RESEARCH ARTICLE

Risk of alterations in neurodevelopment in infants and preschool children with cancer

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Abstract

Background: *Some cancer survivors experience difficulties with concentration, attention, and memory; however, there are no studies on neurodevelopment in patients under 5 years of age who are undergoing cancer treatment. Our aim was to evaluate neurodevelopment in cancer patients under 5 years of age using the Early Development Instrument (EDI) test, considering factors such as nutritional status, type of cancer, and treatment effect.* **Methods:** *A cross-sectional study was conducted from February 2018 to March 2019. Patients with cancer diagnoses outside the central nervous system in any phase of cancer treatment were included.* **Results:** *A total of 45 patients were included. Regarding fine motor skills, 28% of patients with retinoblastoma and 23% of patients with leukemia or lymphoma had a risk of developmental delay compared to 0% of patients with solid tumors (p = 0.025).The final results showed that 19 (42.2%) patients had normal neurodevelopment (gray), 7 (15.5%) had a delay in neurodevelopment (light gray), and 19 (42.2%) had a risk of developmental delay (black). Regarding developmental delay, 52% of patients in the leukemia and lymphoma group, 71% in the retinoblastoma group, and 23% in the solid tumor group presented developmental delay (p = 0.06).* **Conclusions:** *The risk of delay and lag in neurodevelopment is common in cancer patients under 5 years of age undergoing treatment. However, more studies are required to evaluate the effect of treatment on this group of patients as it may be affected by various factors.*

Keywords: *Neurodevelopmental disorders. Neoplasm. Child development. Drug therapy.*

Riesgo de alteraciones en el neurodesarrollo en infantiles y prescolares con cáncer

Resumen

Introducción: *En algunos pacientes supervivientes de cáncer se presentan dificultades de concentración, atención y memoria, sin embargo no hay estudios en relación al neurodesarrollo en pacientes menores de 5 años que se encuentran en tratamiento oncológico. Por lo que el objetivo fue valorar el neurodesarrollo en pacientes con cáncer durante el tratamiento oncológico mediante la prueba EDI tomando en cuenta diversos factores como su estado nutricional, tipo de cancer, y el efecto del tratamiento.* **Métodos:** *Se realizó un estudio transversal, de febrero de 2018 a marzo de 2019. Se incluyeron*

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pacientes mayores de 1 año y menores de 5 años con diagnóstico de cáncer fuera del sistema nervioso central, en tratamiento oncológico. **Resultados:** *Se incluyeron 45 pacientes. En el área motor fina el 28% de los pacientes con retinoblastoma y 23% con leucemias y linfomas se encontraron en rojo (retraso) en comparación con 0% de los pacientes con tumores sólidos (p = 0.025). En el resultado global se encontró que 19 (42.2%) pacientes tuvieron neurodesarrollo normal (gris), 7 (15.5%) rezago en el neurodesarrollo (gris claro) y 19 (42.2%) con riesgo de retraso en el desarrollo (negro). De los pacientes que presentaron riesgo de retraso el 52% fueron del grupo de leucemias y linfomas, el 71% en el grupo de retinoblastoma y el 23% del grupo de tumores sólidos (p = 0.06).* **Conclusiones:** *La presencia de riesgo de retraso y rezago en el neurodesarrollo es frecuente en menores de 5 años con diagnóstico de cáncer. Se requieren más estudios, para evaluar el efecto del tratamiento en este grupo de pacientes, ya que pueden influir diversos factores.*

Palabras clave: *Alteraciones en el neurodesarrillo. Neoplasias. Desarrollo infantil. Quimioterapia.*

Introduction

Childhood neurodevelopment is a dynamic process in which the child learns to process complex levels of movement, thoughts, feelings, and relationships from birth to 5 years of age[1]. It is difficult to separate physical factors from psychosocial factors. Neurodevelopmental evaluation aims to identify and quantify the level of maturation reached by a child compared with other children in their age group, allowing the identification of alterations and establishing an individualized profile of the strengths and weaknesses of the evaluated domains[1].

Worldwide, nearly 200 million children under 5 years of age are at risk of not achieving their full developmental potential[2]. There are several causes, such as lack of stimulation, diseases of the central nervous system (CNS), malnutrition, and various treatments, including chemotherapy.

Cancer in children is currently a national public health problem as it is the second leading cause of death in patients under 15 years of age. In Mexico, the incidence of childhood cancer was 150.1 cases/million in 2015; approximately 20% of these cases occurred in patients under 5 years of age. The primary diagnoses at this age are leukemia, CNS tumors, lymphoma, sarcoma, kidney, and liver tumors[3].

In general, patients with cancer diagnoses receive multimodal treatment with chemotherapy, radiotherapy, and surgery; the route of administration and doses depend on the specific diagnosis[4].

Systemic and intrathecal chemotherapy leads to a wide range of cognitive symptoms, including slow information processing and difficulties with concentration, attention, and memory[5]. The etiology of cognitive impairment after chemotherapy remains unknown. However, several mechanisms have been postulated, such as direct neurotoxic effects, hormonal changes, immune dysregulation, coagulation in the small vessels of the CNS, and genetic predisposition to the development of cognitive impairment[6]. In a systematic review published in 2008, 13 articles on pediatric patients with leukemia were included in the study. Leukemia survivors showed lower fine motor skills, verbal memory, processing speed, and academic performance. However, there were no effects on visual memory and visual-motor skills[5].

Neurocognitive difficulties as a result of chemotherapy have been documented primarily in adult survivors of childhood cancer. However, most pediatric studies have focused on children with tumors in the CNS[7]. To date, evidence of late cognitive sequelae has been found in childhood cancer survivors with brain tumors and acute lymphoblastic leukemia[8]. It has been proposed that chemotherapy can cause neurological damage through various neurobiological mechanisms, including damage to the blood–brain barrier and stimulation of a neuroinflammatory response[5]. Likewise, a high frequency of neurological alterations has been observed in leukemia survivors compared to their family controls[9]. However, there is no literature on the effect of cancer treatment (chemotherapy, radiotherapy, or surgery) on neurodevelopment in patients under 5 years of age.

This study aimed to analyze neurodevelopment using the Early Development Instrument (EDI) test in cancer patients under 5 years of age at the *Instituto Nacional de Pediatría* (National Institute of Pediatrics), considering their nutritional status as the initial data for this understudied problem.

EDI test

The EDI test is a screening tool designed and validated in Mexico to detect neurodevelopmental problems in children under 5 years of age. This test has a sensitivity of 81% and a specificity of 61%. The frequency of neurodevelopmental lag in healthy pediatric

patients in Mexico is 10-20%, and the neurodevelopmental delay occurs in 2-4% of patients. It is currently considered the most accurate tool for the timely detection of neurodevelopmental problems in the Mexican population[10-13].

The EDI test assesses motor, language, social, adaptive, and cognitive development and categorizes them into four subgroups: gross motor, fine motor, language, and social development. It is divided into three blocks. Block 1 includes the age group, which is divided into 14 groups ranging from 1 to 60 months (Table 1), calculation of the corrected age in children born before 37 weeks of gestation in children under 2 years of age, and patient data identification[1]. Block 2 includes the evaluation of biological risk factors (attendance at two or fewer prenatal consultations, presence of bleeding, infection, hypertension, or systemic disease during pregnancy, gestation less than 34 weeks, birth weight ≤ 1,500 g, delay in breathing and circular cord during delivery, hospitalization in the neonatal intensive care unit or hospitalization before the 1st month of life lasting more than 4 days, maternal age < 16 years old at the time of delivery); warning signs (set of signs and symptoms or the absence of specific milestones that may suggest a developmental problem) or alarm signs (clinical expression of a problem or deviation from the normal pattern of development that requires further evaluation); areas of development; and neurological examination where it is determined if the patient has any alteration in the mobility of any part of the body, if the patient has any alteration or asymmetry in the mobility of the eyes or facial expression, or if the head circumference is above or below two standard deviations for his/her age. Block 3 includes the final grade of normal development (gray), developmental lag (light gray), and risk of developmental delay (black) (Table 2).

Table 1. Age groups according to the EDI test

Group	Age
Group 1	1 month to 1 day before 2 months
Group 2	2 months to 1 day before 3 months
Group 3	3 months to 1 day before 4 months
Group 4	4 months to 1 day before 5 months
Group 5	5 months to 1 day before 7 months
Group 6	7 months to 1 day before 10 months
Group 7	10 months to 1 day before 13 months
Group 8	13 months to 1 day before 16 months
Group 9	16 months to 1 day before 19 months
Group 10	19 months to 1 day before 25 months
Group 11	25 months to 1 day before 31 months
Group 12	31 months to 1 day before 37 months
Group 13	37 months to 1 day before 49 months
Group 14	49 months to 1 day before 60 months

EDI: Early Development Instrument.

Methods

A cross-sectional study was carried out in the Oncology Department of the National Institute of Pediatrics from February 2018 to March 2019. Patients > 1 month and < 5 years diagnosed with cancer outside the CNS were included. All patients were in an active phase of cancer treatment, which differed by drug and time according to the neoplasia type. Lumbar puncture was performed in patients with leukemia or lymphoma, and magnetic resonance imaging was performed in patients with solid tumors to rule out CNS involvement. The patients were divided into three groups according to their diagnosis: leukemia or lymphoma, solid tumors outside the CNS, and retinoblastoma. Patients with metastatic disease in the CNS, neurological diseases, or a history of skull trauma or CNS infections before their oncological diagnosis were excluded from the study. Patients with congenital abnormalities and severe hearing or visual problems at the time of diagnosis were also excluded from the study.

The parents of the patients were invited to participate in the study after providing written informed consent. The Research Ethics Committee of the National Institute of Pediatrics approved the study (No. 015/2018). Three researchers performed the EDI test. Standardization was carried out by an expert on the test who conducted exercises to apply the EDI test and repeated these exercises 2 months later (Kappa = 0.94 for its performance). The test manual, single answer sheet, and necessary materials were used. All patients were evaluated in the outpatient clinic or the oncology service. As part of their initial evaluation, patients underwent a nutritional assessment by a nutritionist at the time of their diagnosis, which included weight and height measurements; these were compared with the World Health Organization (WHO) weight indicators for age, weight-for-height, and height-for-age. The WHO weight-for-height and height-for-age z-score criteria were used to classify malnutrition: a height-for-age z-score < -2 indicated chronic malnutrition and a weight-for-height

Table 2. Global rating of the EDI test

Normal development Yellow	Developmental lag Green	Developmental delay risk Red
The patient meets all the milestones and skills expected for his age group. The patient has no warning signs or alterations in the neurological examination.	The patient does not meet the milestones and abilities expected for his age group but has achieved the milestones of the previous age group. The patient has no warning signs and the neurological examination is normal.	The child does not adequately meet the milestones and abilities expected for his age group and has not achieved the milestones of the previous group. The patient has warning signs or the neurological examination is abnormal.

EDI: Early Development Instrument.

z-score < -2 indicated acute malnutrition. Patients who were assessed as having developmental delay, according to the neurodevelopmental evaluation, were sent for evaluation by a pediatric neurologist. Descriptive statistics were used for statistical analyses, including means and standard deviations for continuous quantitative variables and frequencies and proportions for qualitative variables. The odds ratio (OR), Mantel–Haenszel test, χ^2 test, and analysis of variance were used to compare the two groups. In addition, multiple logistic regression analysis was performed, with the OR and 95% confidence interval obtained to determine association. The analysis was performed with STATA 18.1.

Results

Forty-five patients were enrolled in the study, of whom 25 (55.5%) were male. The mean age was 26.8 (4-59) months. Regarding the oncological diagnosis, 17 (37.7%) patients had leukemia or lymphoma, 7 (15.5%) retinoblastoma, and 21 (46.6%) solid tumors outside the CNS (Table 3). In the evaluation of their nutritional status carried out at the time of diagnosis, we found that 48.8% had some degree of chronic malnutrition, and 39.8% had acute malnutrition (p = 0.37). There were no differences in nutritional stage, oncological diagnosis, or neurodevelopmental delay when considering weight. In patients with leukemia, there was a relation between low height (chronic malnutrition) and lag in neurodevelopment, with an OR of 0.66 (0.04–9.4) and p = 0.04 (Tables 4 and 5).

According to the age group, the following were included: 11 (24.4%) patients from group 14, 5 (11.1%) from group 13, 10 (22.2%) from group 12, 9 (20%) from group 11, 7 (15.5%) from group 10, and 1 (2.2%) each from groups 9, 7, and 4.

In all, 31% of patients had some biological risk factor, which was more common in patients with solid tumors (n = 9). Thirteen (28.8%) patients presented with alarm signals, of whom 9 (52%) were in the leukemia and lymphoma group (p = 0.002). Three patients (6.6%) from the retinoblastoma group presented abnormal findings in the neurologic assessment at the time of the test (p = 0.002).

Regarding the areas of development, for gross motor skills, 31 (68.8%) patients had normal development (gray), and 35 patients (77.7%) had normal fine motor development. In the language area, 33 patients (73.3%) had normal neurodevelopment; in the social area, 41 patients (91.1%) were reported as gray; and in the cognitive area, 13 patients (26%) were found as gray (only 19 patients were evaluated by their age group). It was observed that 95% of patients with solid tumors had normal fine motor development (gray) compared to 58% of patients with leukemia or lymphoma and 85% of patients with retinoblastoma (p = 0.42). In this same area, 28% of patients with retinoblastoma and 23% of patients with leukemia or lymphomas had a risk of developmental delay (black) compared to 0% of patients with solid tumors (p = 0.025) (Table 6). The final test results showed that 19 (42.2%) patients had normal neurodevelopment, 7 (15.5%) had a lag in neurodevelopment, and 19 (42.2%) had a risk of delayed development. Regarding developmental delay, 52% of patients in the leukemia and lymphoma group, 71% in the retinoblastoma group, and 23% in the solid tumor group presented developmental delay (p = 0.06); (Fig. 1).

Multiple logistic regression analysis was performed, and it was observed that patients who presented alarm signals at the time of the evaluation had severe chronic malnutrition (OR: 13.8, 95% CI: 1.42-131.1; p = 0.022) and a diagnosis of leukemia or lymphoma (OR: 10.87, 95% CI: 1.94-60.95; p = 0.007).

Discussion

Pediatric cancer survivors have long-term sequelae that can affect their quality of life and prevent their full

Table 3. Clinical characteristics of cancer patients under 5 years of age at the National Institute of Pediatrics 2018-2019

Clinical characteristics	Measurement scale	p
Age of the patient at the time of evaluation	Mean (standard deviation)	
Leukemia and lymphoma (n = 17)	34.9 (11.56)	
Retinoblastoma (n = 7)	43.5 (11.9)	0.21
Solid tumors (n = 21)	32.7 (15.1	
Sex	**n (%)**	
Female	20 (44.5)	0.29
Male	25 (55.5)	
Oncological diagnosis	**n (%)**	
Acute lymphoblastic leukemia	15 (33.33)	0.00
Rhabdomyosarcoma	6 (13.33)	
Retinoblastoma	7 (15.55)	
Langerhans cell histiocytosis	5 (11.11)	
Liver tumors	3 (6.66)	
Germinal tumor	2 (4.44)	
Neuroblastoma	2 (4.44)	
Wilms tumor	2 (4.44)	
Non-Hodgkin's lymphoma	1 (2.22)	
Osteosarcoma	1 (2.22)	
Hodgkin lymphoma	1 (2.22)	

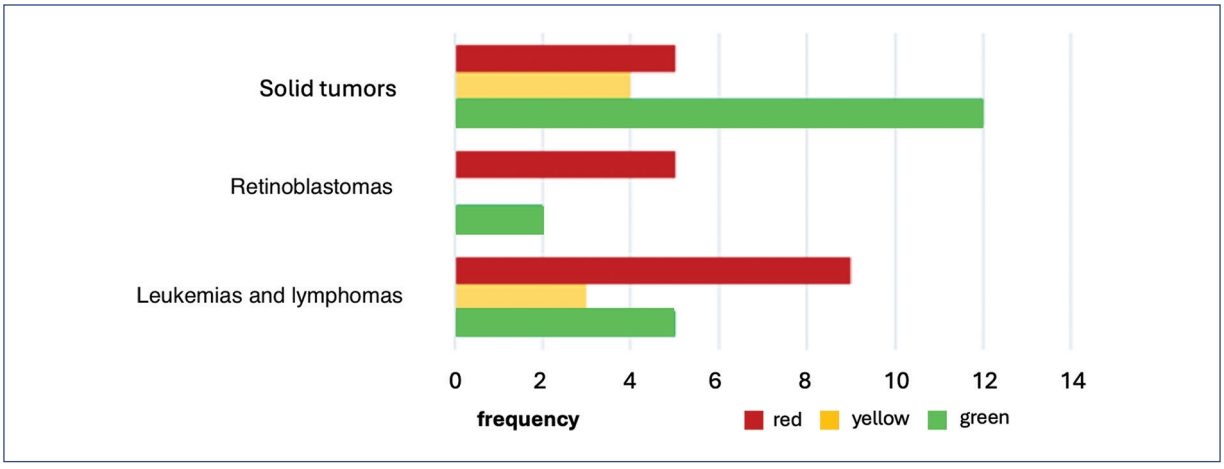

Figure 1. Global result of the early development instrument test in cancer patients under 5 years of age at the National Institute of Pediatrics 2018-2019.

development. A study published by Tuhan in 2018 evaluated 68 surviving patients of acute lymphoblastic leukemia in childhood, who was compared with their siblings as a control group. It was observed that 82.4% had an alteration in neurocognitive functions detected by physical examination, magnetic resonance imaging,

Table 4. Nutritional evaluation at the time of diagnosis of cancer patients under 5 years of age at the National Institute of Pediatrics 2018-2019

Variable	Leukemia and lymphomas Frequency (%) (n = 17)	Retinoblastomas Frequency (%) (n = 7)	Solid tumors Frequency (%) (n = 21)	p
Height				
Normal	5 (29)	5 (71)	12 (57)	0.11
Mild chronic malnutrition	5 (29)	-	4 (19)	0.36
Moderate chronic malnutrition	4 (23)	1 (14)	2 (9)	0.56
Serious chronic malnutrition	2 (11)	1 (14)	3 (14)	1.00
Size	1 (5)	-	-	-
Weight				
Normal	8 (47)	6 (85)	12 (57)	0.28
Mild acute malnutrition	7 (41)	1 (14)	5 (23)	0.40
Moderate acute malnutrition	-	-	1 (4)	-
Severe acute malnutrition	1 (5)	-	3 (14)	0.64
Overweight	1 (5)	-	-	-

Table 5. Analysis of the relation between chronic malnutrition and lag or delay in neurodevelopment in patients with leukemia/lymphoma or solid tumors

Tumor	Chronic malnutrition	Delay OR (CI 95%)	p	Lag OR (CI 95%)	p
Leukemias and lymphomas					
	Mild	2 (0.11-35.8)	0.63	0.44 (0.03-5.5)	0.53
	Moderate			0.66 (0.04-9.4)	0.04
Solid tumors					
	Mild	11 (0.64-187.1)	0.09		
	Moderate			3 (0.14-64.2)	0.48
	Severe	5.5 (0.23-129)	0.29	1.5 (0.09-23)	0.77

OR: odds ratio; CI: confidence interval.

or neurocognitive tests compared to 29% in the control group ($p < 0.001$). The evaluations included intellect, attention, memory, judgment, learning skills, and execution, as well as structural or functional alterations. These patients had received treatment with intrathecal chemotherapy, systemic chemotherapy, and sometimes radiation therapy to the CNS[9]. They were found to have alterations in intellectual functioning, particularly in non-verbal intelligence, mathematical achievement, visual-motor integration, processing speed, attention, and executive functioning. Likewise, retrospective reports in childhood cancer survivors suggest that diagnosis at a younger age increases the risk of neurocognitive deficits. However, despite this information, there are no published studies evaluating neurodevelopment in cancer patients under 5 years of age during their treatment. Instead, most studies have been conducted on patients already in surveillance and considered survivors.

The current study found that 42.2% of children had a risk of delay, and 15.5% had a lag in neurodevelopment. In previous reports in a healthy Mexican population, a frequency of 20% neurodevelopmental lag and 4% risk of neurodevelopmental delay have been reported, indicating that this type of is more frequent in patients during cancer treatment. The areas of most frequent alterations were fine motor, gross motor, and language. Notably, developmental delay was observed more frequently in patients diagnosed with leukemia and lymphoma compared to solid tumors and retinoblastoma. In 2018, a study was published on 235 leukemia patients undergoing treatment with systemic and intrathecal chemotherapy. The study focused on analyzing biomarkers of myelin degradation in cerebrospinal fluid (such as myelin basic protein [MBP], nerve growth factor [NGF], and glial fibrillary acidic protein [GFAP]), as well as neuroinflammation by chitotriosidase. The results showed elevated levels of MBP and GFAP after the

Table 6. Evaluation of areas of development according to pathology of cancer patients under 5 years of age at the National Institute of Pediatrics, 2018-2019

Evaluation	Leukemia and lymphomas Frequency (%) (n = 17)	Retinoblastomas Frequency (%) (n = 7)	Solid tumors Frequency (%) (n = 21)	p
Biological risk	4 (0.23)	1 (0.14)	9 (0.42)	0.37
Neurological examination				
Yellow	17 (1.00)	4 (0.57)	21 (1.00)	0.002*
Red	-	3 (0.42)	-	
Alarm				
Yellow	8 (0.47)	4 (0.57)	20 (0.95)	0.002*
Red	9 (0.52)	3 (0.42)	1 (0.04)	0.002*
Gross motor				
Yellow	10 (0.58)	6 (0.85)	15 (0.71)	0.42
Green	5 (0.29)	-	4 (0.19)	0.36
Red	2 (0.11)	1 (0.14)	2 (0.09)	1.00
Fine motor				
Yellow	10 (0.58)	5 (0.71)	20 (0.95)	0.017*
Green	3 (0.17)	-	1 (0.04)	0.35
Red	4 (0.23)	2 (0.28)	-	0.025*
Language				
Yellow	12 (0.70)	6 (0.85)	15 (0.71)	0.81
Green	4 (0.23)	-	4 (0.19)	0.50
Red	1 (0.05)	1 (0.14)	2 (0.09)	0.80
Social				
Yellow	16 (0.94)	6 (0.85)	19 (0.90)	0.80
Green	1 (0.05)	-	1 (0.04)	1.00
Red	-	1 (0.14)	1 (0.04)	1.00
Cognitive				
Yellow	3 (0.42)	4 (0.80)	6 (0.85)	0.18
Green	3 (0.42)	1 (0.20)	1 (0.14)	0.35
Red	1 (0.14)	-	-	-
Global Result				
Yellow	5 (0.29)	2 (0.28)	12 (0.57)	0.18
Green	3 (0.17)	-	4 (0.19)	0.73
Red	9 (0.52)	5 (0.71)	5 (0.23)	0.06

*Significative p-value.

consolidation treatment. The number of intrathecal therapies was positively correlated with the elevation of NGF level (r = 0.19, p = 0.005). It was concluded that neuronal damage was associated with intrathecal therapy[14]. Therefore, we consider that the administration of both systemic and intrathecal treatment with chemotherapy led to the observed neurodevelopmental alterations in our patients. However, we did not analyze or demonstrate an association in this study.

There appears to be a connection between delayed development in leukemia patients and short stature. This may be linked to inadequate growth and brain development, as indicated by multiple studies. We suggest conducting additional research into brain development, growth, and developmental delays (using the EDI test). Moreover, it may be possible to establish a connection with abnormal data when the EDI test is conducted.

A significant limitation of this study was that the patients were evaluated while undergoing active cancer treatment. Consequently, it remains uncertain whether the patients exhibited neurodevelopmental delays or impairments before their cancer diagnosis or the administration of chemotherapy. Although patients with primary tumors or metastases in the CNS were excluded from the study, neurological examination at the time of evaluation revealed alterations in three patients. Despite this limitation, this study is the first to assess neurodevelopment in a population of Mexican patients with an oncological diagnosis. At present, we are evaluating patients at the time of diagnosis, before they receive chemotherapy

treatment, to determine if any observed neurodevelopmental alterations are secondary to the neoplasm itself, despite its location outside the CNS, or if they are attributable to the effects of cancer treatment on the brain.

Conclusions

Neurodevelopmental delays and impairments are common among cancer patients under the age of 5. Various factors can influence child development, including nutrition, biological risk factors, and the malignancy itself. The impact of oncologic therapy on neurodevelopment extends beyond the scope of this study. Therefore, further research is necessary to evaluate the effects of these treatments on this population.

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Conflicts of interest

The authors declare no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have used generative artificial intelligence, specifically (SPSS) in the writing of this manuscript and/or in the creation of images, graphics, tables, or their corresponding captions (Fig. 1).

References

1. Rizzoli-Córdoba A, Delgado-Ginebra I. Pasos para transformar una necesidad en una herramienta válida y útil para la detección oportuna de problemas en el Desarrollo infantil en México. Bol Med Infant Mex. 2015;72:420-8.
2. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369:60-70.
3. Rivera-Luna R, Velasco-Hidalgo L, Zapata-Tarrés M, Cárdenas-Cardós R, Aguilar-Ortiz MR. Current outlook of childhood cancer epidemiology in a middle-income country under a public health insurance program. Pediatr Hematol Oncol. 2017;34:43-50.
4. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 7th ed. Netherlands: Wolters Kluwer; 2016. p. 587-603.
5. Peterson CC, Johnson CE, Ramirez LY, Huestis S, Pai AL, Demaree HA, et al. A meta-analysis of the neuropsychological sequelae of chemotherapy-only treatment for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer. 2008;51:99-104.
6. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer. 2007;7:192-201.
7. Lyer NS, Balsamo LM, Bracken MB, Kadan-Lottick NS. Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. Blood. 2015;126:346-53.
8. Moore BD 3rd. Neurocognitive outcomes in survivors of childhood cancer. J Pediatr Psicol. 2005;30:51-63.
9. Turhan AB, Tülin Finda S, Yarar C, Nazli SakaLLi E, Özdemir ZC, Bör O. Neurocognitive consequences of childhood leukemia and its treatment. Indian J Hematol Blood Transfus. 2018;34:62-9.
10. Rizzoli-Córdoba A, Schnaas-Arrieta L, Liendo-Vallejos S, Buenrostro-Márquez G, Romo-Pardo B, Carreón-García J, et al. Validación de un instrumento para la detección oportuna de problemas de Desarrollo en menores de 5 años en México. Bol Med Hosp Infant Mex. 2013;70:195-208.
11. Rizzoli-Córdoba A, Schnaas-Y-Arrieta L, Ortega-Riosvelasco F, Rodríguez-Ortega E, Villasís-Keever MA, Aceves-Villagrán D, et al. Child development evaluation test analysis by field improves detection of developmental problems in children. Bol Med Hosp Infant Mex. 2014;71:154-162.
12. Rizzoli-Córdoba A, Campos-Maldonado MC, Vélez-Andrade VH, Delgado-Ginebra I, Baquero-Hernández CI, Villasís-Keever MA, et al. Evaluación diagnóstica del nivel de desarrollo en niños identificados con riesgo de retrado mediante la prueba de Evaluación de Desarrollo Infantil. Bol Med Hosp Infant Mex. 2015;72:397-408.
13. Comisión Nacional para la Protección Social en Salud. Manual para la Aplicación de la Prueba Evaluación del Desarrollo Infantil "EDI". 1st ed. Mexico: Comisión Nacional para la Protección Social en Salud; 2013.
14. Cheung YT, Khan RB, Liu W, Brinkman TM, Edelmann MN, Reddick WE, et al. Association of cerebrospinal fluid biomarkers of central nervous system injury with neurocognitive and brain imaging outcomes in children receiving chemotherapy for acute lymphoblastic leukemia. JAMA Oncol. 2018;4:e180089.