Neuropsychomotor development and functional skills in preschool children with liver diseases

Desenvolvimento neuropsicomotor e habilidades funcionais em pré-escolares com doenças hepáticas

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Date of first submission: September 15, 2021
Last received: February 8, 2022
Accepted: August 19, 2022
Associate editor: Ana Paula Cunha Loureiro

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Abstract

Introduction: Children with chronic liver diseases are exposed to biological and/or environmental risk factors that can compromise their neuromotor acquisition and development of functional skills. **Objective:** To describe the neuropsychomotor development (NPMD) and functional skills of children with chronic liver diseases. **Methods:** Cross-sectional, descriptive and exploratory study carried out with children up to 6 years old who were selected at a reference hospital in the state of Bahia, Brazil, from November 2019 to March 2020. Children in outpatient care with clinical, laboratory and histological diagnosis compatible with chronic liver disease were considered eligible. The instrument for assessing neuropsychomotor development was Denver II. Functional skills were obtained by applying the Pediatric Evaluation of Disability Inventory computer-adaptive test (PEDI-CAT) to parents or primary caregivers, Speedy version (Speedy-CAT). **Results:** Of the 34 children with chronic liver disease, 52.9% were female, aged between 4 and 6 years (64%). The results of the Denver II test showed that 68.7% (22/32) of the sample were at risk for NPMD. In the PEDI-CAT, the scores of children with liver disease at risk for NPMD were 60.7 ± 9.1 in the daily activity domains, 57.6 ± 11.8 in mobility and 48.3 ± 6.2 in the social/cognitive domains. **Conclusion:** Children with chronic liver disease are at risk for NPMD, although not presenting impaired functional skills when evaluated by the PEDI-CAT.

Keywords: Child development. Developmental disabilities. End-stage liver disease.

Resumo

Introdução: *Crianças com doenças hepáticas crônicas são expostas a fatores de risco biológicos e/ou ambientais que podem comprometer suas aquisições neuromotoras e o desenvolvimento de suas habilidades funcionais.* ***Objetivo:*** *Descrever o desenvolvimento neuropsicomotor (DNPM) e habilidades funcionais de crianças com doenças hepáticas crônicas.* ***Métodos:*** *Estudo seccional, descritivo e exploratório realizado com crianças de até 6 anos, que foram selecionadas em um hospital de referência do estado da Bahia, Brasil, no período de novembro de 2019 a março de 2020. Foram consideradas elegíveis para o estudo crianças em atendimento ambulatorial, com diagnóstico clínico, laboratorial e histológico compatíveis com doença hepática crônica. O instrumento de avaliação do desenvolvimento neuropsicomotor foi o Denver II. As habilidades funcionais foram obtidas pela aplicação do Inventário de Avaliação Pediátrica de Incapacidade Testagem Computadorizada Adaptativa (PEDI-CAT) aos pais ou cuidadores principais, versão rápida (Speedy-CAT).* ***Resultados:*** *Das 34 crianças com hepatopatias crônicas, 52,9% eram do sexo feminino, com idade entre 4 e 6 anos (64%). Os resultados do teste de Denver II demonstraram que 68,7% (22/32) da amostra apresentaram risco para DNPM. No PEDI-CAT, os escores das crianças hepatopatas com risco para DNPM foram de 60,7 ± 9,1 nos domínios atividade diária, 57,6 ± 11,8 em mobilidade e 48,3 ± 6,2 em social/cognitivo.* ***Conclusão:*** *Crianças com hepatopatias crônicas apresentam risco para DNPM, apesar de não possuírem comprometimento de suas habilidades funcionais quando avaliadas pelo PEDI-CAT.*

Palavras-chave: *Desenvolvimento infantil. Deficiências do desenvolvimento. Doença hepática terminal.*

Introduction

Technological-scientific advances in the field of health have enabled different types of clinical-surgical management in children with liver diseases. This has reflected in survival and better quality of life in individuals with irreversible and fatal liver diseases; however, even when undergoing surgery, these procedures often do not represent a definitive cure for the underlying disease, making these children continue to be monitored by a physician.[1] In the course of these diseases, it is known that a liver that is unable to metabolize cerebral toxicity blood substances can interfere with neuropsychomotor development (NPMD), as it exposes this neurological system during development.[2]

Neuropsychomotor development (NPMD) is characterized as a progressive acquisition of motor and psycho-cognitive skills, which occurs in an orderly and sequential way, progressing in the cephalocaudal and proximal to distal directions.[3] This dynamic process allows the child to acquire new behaviors (skills in the gross, fine, cognitive, and emotional motor domain) and modify old patterns.[4] Development can be assessed with several instruments by members of the pediatric multidisciplinary team. The Denver Screening Test II (TTDII) is a screening method for child developmental risk that assesses skills in the domains of social and personal behavior, language and motor skills, recommended as typical of developmento.[4,5] Children with liver diseases are exposed to biological risk factors inherent to liver diseases such as pain, ascites, nutritional disorders, medication use, hospitalizations, absences from school and/or family members and routine changes. They are often of low socioeconomic class and the confluence of these factors can compromise the acquisition of cognitive, motor and language skills, resulting in limitations of functional abilities.[5,6]

Some functional activities such as self-care (dressing, eating, performing personal hygiene), mobility activities (basic movements and transfers, standing and walking), social/cognitive function tasks (communication, behavior, attention, playing with games and toys),[7-9] all these skills can be evaluated by specific instruments. The Pediatric Evaluation of Disability Inventory computer-adaptive test (PEDI-CAT) investigates the functional performance of children and youth with any diagnosis. It can be answered by parents or main caregivers or even by health professionals or educators who live with the child.[7]

It is well described in the literature that children with chronic liver disease have a deficit in the NPMD,[2,10-12] however few studies have evaluated the functional skills in this population.[13,14] To date, no other studies were found in which the PEDI-CAT has been used in children and adolescents with liver disease. Therefore, the present study aimed to describe the neuropsychomotor development and functional skills of children with chronic liver diseases.

Methods

Type of study and sample characterization

Cross-sectional, descriptive and exploratory study carried out between November 2019 and March 2020, consisting of a convenience sample of 34 children with chronic liver disease aged between 6 months and 6 years, selected at the Pediatric Gastroenterology and Hepatology Outpatient Clinic of a hospital in reference of the state of Bahia. This project was approved by the Research Ethics Committee of the Institute of Health Sciences, ISC/UFBA (opinion number 3.695.203).

Children in outpatient care, with a clinical, laboratory (low albumin level, prolonged prothrombin time and hypergammaglobulinemia) and histological diagnosis compatible with chronic liver disease with or without liver transplantation were considered eligible for the study. Children with any neurological, psychiatric or other chronic diseases, traumatic brain injury, meningitis, syndromes, with visual or hearing impairment, born with low birth weight (< 2,500 g), who were unable to perform the Denver test or who did not collaborate in the realization of the test were excluded.

Instruments and procedures

The children were evaluated on the day of their routine outpatient consultation. For data collection, a questionnaire was applied by a trained and experienced professional, responsible for the sector, consisting of the thematic blocks described later.

Anthropometric measurements were used to assess the children's nutritional status. The growth curve of body mass index (BMI) x ages developed by the World Health Organization (WHO) was used, which are adopted by the Ministry of Health (children aged 0-5 years WHO 2006, and 5-19 years WHO 2007).[15] To measure the children's weight and height, a mechanical anthropometric medical scale from the Welmy V® brand was used.

The assessment of family income was carried out through the application of a questionnaire, using the classification of the Brazilian Association of Research Companies (APEB), whose market division is defined by economic classes, in which the "A1" class represents the highest family income; and class "E", lower family income.[16] A questionnaire developed by the authors was also applied addressing the following variables: sex, age child's education, number of siblings, birth weight, clinical diagnosis, age at diagnosis, and time of liver disease.

The development assessment instrument used was the Denver II, applied to all children by the same qualified physical therapist. This instrument dichotomously classifies into suspect/risk for development or normal and contains 125 items, presented in four domains: personal-social, fine-adaptive motor, language and gross motor.[17] The assessment is non-invasive, easy to apply and very similar to children's everyday games, such as playing ball and playing with dolls. The screening was applied only once, in a playful way, through direct testing of skills and observation of behavior. The duration of the evaluation was on mean 20 minutes.

When applying the Denver II test, the child's age is calculated and then a vertical line is drawn on the specific sheet of the instrument, then when the procedures referring to this age group are applied in all domains. The child is classified as "normal" when he shows no "delay" or, at most, a "caution" in every test; if it presents one or more signs of "caution" and/or one or more "delays", it is classified as suspicion/risk for alteration of the NPMD.

The children's functional abilities were obtained by applying the Pediatric Evaluation of Disability Inventory computer-adaptive test (PEDI-CAT) to parents or primary caregivers. The instrument software was installed on the researchers' computer and the Speedy version (Speedy-CAT) was administered. This version manages five to fifteen items per domain. The PEDI-CAT describes the functional performance of children between 6 months and 20 years of age, in addition to their independence and need for environmental adaptations to perform specific activities. The PEDI-CAT measures function in four domains: activities of daily living, mobility, social/cognitive and responsibility. However, the domain "responsibility" was not applied in this sample, as it is a domain that assesses the management of daily activities, making it more difficult and requiring a higher chronological age than the current sample. The response scale for the PEDI-CAT domains of daily activities, mobility and social/cognitive is:

1. "Unable", if the child cannot do it, does not know how or is too young.

2. "Hard" if the child does it with a lot of help, extra time or effort.

3. "A little hard", if the child does it with a little help, extra time or effort.

4. "Easy", if the child does it without help, extra time or effort or the skills of the

child exceeds that level.

5. "I don't know", if the respondent reports not knowing; however, this level of response is not calculated in the score and another item is administered instead.

The score was adopted by normative scores, which are presented as T-scores, whose mean for each age group is 50, with a standard deviation of 10; that is, scores between 30 and 70 (the mean + 2 standard deviations) are considered to be within the expected range for the age.[7]

Statistical analysis

The PEDI-CAT domains were computed and the normality of data distribution was attested by the Kolmogorov-Smirnov test. To compare the proportions of each domain of the PEDI-CAT and categories of liver transplantation (native or transplanted), according to DENVER II classes, bivariate linear regression analysis was performed, adopting a statistical significance of 5%.

Data were analyzed using the statistical IBM SPSS software (19.0 for Windows), with quantitative variables presented in measures of central tendency and dispersion (mean, median and standard deviation); categorical variables in absolute and relative frequency.

Results

The sample consisted of 34 children with chronic liver disease, of which 52.9% (18/34) were female, with a mean total age of 3.8 ± 1.5 years (minimum of 9 months and maximum of 6 years). About 79.4% (27/34) did not live in the capital of Bahia. A total of 67.6% (23/34) attended school, with 47.1% (16/34) of the sample belonging to economic classes D and E (Table 1).

Regarding the liver diagnosis, about 20.6% (7/34) had extrahepatic bile duct atresia, 17.6% (6/34) had chronic hepatitis and 11.8% (4/34) had cholestatic causes, metabolic and vascular. The category called other diseases consisted of liver diseases that had a low individual frequency. The age at diagnosis had a mean of 1.5 ± 1.3 years, the duration of liver disease was 2.5 ± 1.4 years and the mean number of hospitalizations was 2.3 ± 1.5 (Table 1).

In the BMI x age variable, it was observed that 54.5% (18/34) were eutrophic, followed by 24.2% (8/34) at risk for overweight. The children were born with a mean weight of 2.9 ± 0.83 kg (Table 1).

Table 1 - Sociodemographic and clinical characteristics of the sample of children with liver disease (n = 34)

Characteristics	**Total** n (%)
Sex	
Male	16 (47.1)
Female	18 (52.9)
Age (years)*	3.80 ± 1.51
0 to 2	5 (14.7)
> 2 to 4	7 (20.6)
> 4 to 6	22 (64.7)
Origin	
Salvador	7 (20.6)
Other cities	27 (79.4)
Education	
Does not attend school	11 (32.4)
Attends school	23 (67.6)
APEB Class	
B1	1 (2.9)
B2	4 (11.8)
C1	1 (2.9)
C2	12 (35.3)
D and E	16 (47.1)
Diagnosis for chronic liver disease	
Extrahepatic bile duct atresia	7 (20.6)
Chronic hepatitis	6 (17.6)
Autoimmune diseases	2 (5.9)
Cholestatic diseases	4 (11.8)
Metabolic diseases	4 (11.8)
Vascular diseases	4 (11.8)
Other diseases	7 (20.6)
Age at diagnosis (years)*	1.50 ± 1.33
Sickness time (years)*	2.57 ± 1.41
Number of hospitalizations*	2.38 ± 1.56
Body mass index x Age	
Malnutrition	2 (6.1)
Eutrophic	18 (54.5)
Overweight	10 (30.3)
Obesity	3 (9.1)
Birth weight (kg)*	2.93 ± 0.83

Note: *$\overline{X} \pm \sigma$. APEB = Brazilian Association of Research Companies.

The results of the Denver II test showed that about 68.7% (22/32) of the sample was at risk for NPMD. In the association between the Denver and PEDI-CAT instruments, it was found that among children with liver disease at risk for neurodevelopment and with preservation of their native livers, the normative score/ T-Score was 61.7 ± 9.3 for activities daily, 59.5 ± 11.4 for the mobility domain and 48.5 ± 6.3 for the social/ cognitive domain. The present series obtained scores in the daily activity domains of 59.8 ± 8.8, 57.4 ± 10.6 in mobility and 49.2 ± 6.1 in social/cognitive (Table 2).

When stratifying the Denver II domains, about 12.5% (4/32) of children at risk for NPMD were delayed in the personal-social domains, 28.2% (9/32) in the fine motor, followed by 34.4% (11/32) in language and 12.5% (4/32) in the gross motor domain (Table 3).

Table 2 - Neuropsychomotor development (NPMD) and functional skills of children with liver disease from six months to six years of age (n = 34)

Variables (Denver)	PEDI-CAT						DENVER II
	Daily activities T-Score	p-value	Mobility T-Sscore	p-value	Social Cognitive T-Score	p-value	Total n (%)
Native liver							
Without risk	58.1 ± 6.8		57.1 ± 8.3		51.6 ± 6.1		8 (26.7)
NPMD risk	61.7 ± 9.3	0.413	59.5 ± 11.4	1.000	48.5 ± 6.3	0.051	20 (66.7)
Not tested	62.5 ± 4.9		56.0 ± 15.5		45.0 ± 11.3		2 (6.7)
Total children	60.8 ± 8.4		58.6 ± 10.6		49.1 ± 6.5		30 (100)
Transplanted liver							
Without risk	53.0 ± 0.0		51.5 ± 0.7		49.0 ± 1.4		2 (50.0)
NPMD risk	53.0 ± 7.0	1.000	44.5 ± 2.1	0.047*	51.0 ± 2.8	0.465	2 (50.0)
Total children	53.0 ± 4.0		48.0 ± 4.2		50.0 ± 2.1		4 (100)
Total							
Without risk	57.1 ± 6.8		57.2 ± 7.0		52.4 ± 3.7		10 (29.4)
NPMD risk	60.7 ± 9.1	0.293	57.6 ± 11.8	0.928	48.3 ± 6.2	0.079	22 (64.7)
Not tested	62.5 ± 4.9		56.0 ± 15.5		45.0 ± 11.3		2 (5.9)
Total children	59.8 ± 8.8		57.4 ± 10.6		49.2 ± 6.1		34 (100)

Note: PEDI-CAT = Pediatric Evaluation of Disability Inventory computer-adaptive test. Estimates did not include children not tested for DENVER II (n = 32).

Table 3 - Denver II test domains of children with liver disease from six months to six years of age (n = 32)

	DENVER II Domains n (%)			
	Personal-social	Fine motor	Language	Gross motor
Native liver				
Normal	21 (75.0)	12 (42.8)	11 (39.2)	19 (67.7)
Risk	4 (14.3)	9 (32.2)	11 (39.2)	3 (10.7)
Caution	3 (10.7)	7 (25.0)	6 (21.6)	6 (21.6)
Total	28 (100)	28 (100)	28 (100)	28 (100)
Transplanted liver				
Normal	-	4 (100)	3 (75.0)	3 (75.0)
Risk	4 (100)	-	-	-
Caution	-	-	1 (25.0)	1 (25.0)
Total	4 (100)	4 (100)	4 (100)	4 (100)
Total				
Normal	25 (78.1)	15 (46.8)	14 (43.8)	22 (68.7)
Risk	4 (12.5)	9 (28.2)	11 (34.4)	4 (12.5)
Caution	3 (9.3)	8 (25.0)	7 (21.8)	6 (18.8)
Total	32 (100)	32 (100)	32 (100)	32 (100)

Note: Estimates did not include two (5.9%; 2/34) children not tested for DENVER II.

Discussion

In the present study, most children were at risk for neuropsychomotor development; however, those at risk for NPMD did not show impairments in their functional skills. The diagnosis of liver disease occurred in the first two years (critical period of brain development) and the duration of the disease had a mean of two and a half years. Considering that the children are preschoolers, they had spent half their lives in liver distress.

Gilmour et al.,[13] in 2009, used the Bayley II and Wechsler scales to assess the NPMD and the Vineland Adaptive Behavior Scale (VABS) to screen the functional skills of preschool children who underwent liver transplantation. The assessment of adaptive function aims to describe children's functional skills, identifying strengths and difficulties, comparing them with a standardized sample of instruments.[18] Similar to the present study, the authors found developmental delay in their sample; however, the VABS questionnaire answered by the parents seems to have underestimated the mental and cognitive delay scores measured in their population, presenting values within the recommended standard deviations.[13]

In 2017, Gold et al.[14] studied children with chronic liver disease and a mean age of four years. Two groups were evaluated with VABS, transplanted and with native livers, and it was observed that children who underwent transplantation before two years of age were more vulnerable to neuropsychological risks than children with native livers. As for the functional skills data, although the transplanted ones presented lower values, both groups obtained scores compatible with the instrument's standardization, corroborating the findings of the present study.

The PEDI-CAT tested high reliability and validity in children with various types of disabilities and without disabilities;[19] however, Milne et al.,[18] in 2019, compared the PEDI-CAT instrument with VABS (the most commonly used instrument to evaluate functional skill of the children in their day-to-day activities)[7] in preschool children, where most had a diagnosis of autism spectrum disorder. The authors observed that the PEDI-CAT inventory was less sensitive in detecting the need for assistance that these children needed to perform their daily activities.[18] The fact that this instrument does not have subscales makes a more comprehensive assessment impossible and, therefore, could easily mask difficulties in the execution of specific skills in these children, suggesting that the PEDI-CAT is not the most appropriate instrument for young children, that is, in preschool age.[18]

There are differences between performance and competence. Performance is understood as what the children do in their family environment and their environment works as a facilitator, resulting in better functionality. Competence refers to the child's skill to perform activities of daily living, regardless of the influence of the environment.[20,21] While the children in the present study were evaluated by an instrument associated with the skill to perform developmental milestones in a controlled environment, they did not present similar results to an instrument that evaluate performance in their real environments. In a way, these concepts can justify the findings of the present study, like those of the cited studiess.

The results of the current sample can also be attributed to the fact that a questionnaire was applied to caregivers; that is, unlike a neurodevelopmental test where the therapist performs tasks and observes behaviors directly on the children. It is believed that there may be an attempt by parents to deny their children's functional problems, as they could be tired due to the time of treatment they were experiencing.

In 2018, Ng et al.[2] analyzed children undergoing a hepatoportoenterostomy surgical procedure and observed that even those with a successful surgical process remained vulnerable to the risk of physical, motor, cognitive and language delays at 2 years of age. Claudle et al.,[22,23] in their 2010 and 2012 studies, observed that babies with biliary atresia also had NPMD deficits. In the current study, children showed more risk and/or caution in the domains of language, followed by deficits in fine motor skills.

Paula et al.,[24] in 2017, investigated the language deficits of children aged 2 to 7 years who were divided into pre- and post-liver transplant groups. The authors identified that children on the transplant waiting list had greater language deficits and that those transplanted, despite having scores within the normal range, remained below the reference values of the normal population. It is known that language disorders are disorders more common in preschool age;[24] it is believed that several factors in the sample of the present study could contribute to the literature with similar findings in terms of language. In addition to hepatotoxicity at the time of neural maturation, there are environmental factors, such

as low family income, that can influence neurolinguistic acquisition failures.[25] In the current study, almost eighty percent of the children belonged to families with an income of less than two minimum wages. It is important to understand that children need socio-environmental integrity in order to develop their skills.

In the context of chronic liver disease, these children go through several deprivations: they use constant medication, are removed from their family and school routine, undergo interventions to discover diagnoses and treatments, in addition to suffering from the pathophysiological mechanisms of liver diseasess.[11] The dysfunctional liver can produce neurotoxic substances and contaminate the developing neurological system.[26] The longer the liver disease, the greater the possibility of damage to neurodevelopment. In 2005, in a population of children who underwent liver transplantation and evaluated with the Kaufman Assessment Battery for Children (K-ABC), Kaller et al.[27] found that the younger they were to undergo this procedure and the shorter time of exposure to the disease, the better the mental scores. In the present study, children had a mean disease diagnosis of two and a half years and were diagnosed before the second year. Considering a sample of preschool children, it is understood that they can remain for a long period of exposure to dysfunctional hepatic metabolic substances. This fact may reflect on the impairment of family dynamics, as the search for treatment, clinical manifestations of liver diseases and recurrent hospitalizations make these children inopportune to have a typical life.

In children with liver disease with characteristics similar to the present study sample (homogeneous), the data may have reproducibility or internal validity. On the other hand, in populations of children with liver disease with very different (heterogeneous) etiologies, the present study may not have direct reproducibility or external validity. The information about this series, however, is of fundamental importance for understanding the consequences of chronic liver diseases in neuropsychomotor development and functional skills, helping health teams in decision-making and advising family members in daily activities with these children and adolescents.

The present study had limitations resulting from the adoption of non-probability sampling and the impossibility of estimating the sample size calculation, which is justified by the fact that the study evaluated an outcome (chronic liver diseases) of low prevalence in children and difficult to determine the population size. These limitations make it impossible to generalize the findings; however, the study provides information that will support the identification of profiles susceptible to sickness and/or worsening of the clinical condition. In addition, although it was a small sample size, the end of data collection coincided with the saturation of patients in the research outpatient clinic. Studies with a larger sample size are suggested, since this will enable the conduction of more robust analyses that allow the testing of associations in multivariate models.

Conclusion

Children with chronic liver disease are at risk for NPMD, despite not having impaired functional skills when assessed by the PEDI-CAT. It was observed that the longer the liver diagnosis and the duration of the disease, the greater the damage to the acquisition of neuromotor and linguistic skills.

Authors´ contributions

JCS, NMPVB and LRS are responsible for all aspects of the work and contributed substantially to the study design, data acquisition, analysis and interpretation, preparation and critical review of the manuscript, and approval of the final version.

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