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ANALYSIS OF THE ODDS RATIO OF DEVELOPMENTAL DELAY IN CHILDREN WITH BILIARY ATRESIA 12 MONTHS AFTER LIVER TRANSPLANTATION

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Background. Liver cirrhosis occurring before 1 year of age can affect a child's development. Liver transplantation is the only radical treatment for decompensated cirrhosis. In biliary atresia, cirrhosis develops during the first months of life. The duration of cirrhosis in biliary atresia may vary from palliative Kasai portoenterostomy (PE) to liver transplantation. Developmental abnormalities in children with biliary atresia have been shown to occur both before and after liver transplantation. Association between duration of liver cirrhosis and psychomotor development of children has been underestimated. **Objective:** to determine the chances of developmental delay in children depending on the cirrhosis persistence duration. **Materials and methods.** The study enrolled 83 children with biliary atresia (47 children underwent palliative Kasai PE, 36 children with liver transplantation did not undergo Kasai PE). All children had their psychomotor development assessed before PE and 12 months after PE using the Griffiths psychomotor developmental scale (translation and adaptation by E.S. Keshishian) for children up to 24 months of age. Statistical analysis was performed by calculating odds ratios with 95% confidence intervals. **Results**. Comparative analysis showed that in the subgroup of children who underwent Kasai PE, cirrhosis persistence before transplantation was 2.6 months longer than in children without Kasai PE ($p = 0.011$). The odds of developmental delay in preparation for liver transplantation were 3.3 times higher in the subgroup of children who underwent Kasai palliative PE compared to children without palliative (95%, CI 1.35–8.31). The odds of developmental delay 12 months after liver transplantation were 4.4 times higher in the subgroup of children who underwent palliative Kasai PE than in children without the palliative care (95% CI 1.54–12.5). **Conclusion**. Children who underwent liver transplantation after palliative surgical treatment had lower levels of psychomotor development than children without palliative Kasai PE both before and 12 months after liver transplantation ($p = 0.0018$, $p = 0.01$ respectively).

Keywords: liver transplantation, biliary atresia, Kasai portoenterostomy, neuropsychiatric development.

INTRODUCTION

Biliary atresia is one of the most common indications for liver transplantation in children under 1 year of age. According to Gautier [1], the annual number of pediatric orthotopic liver transplants (OLTx) in the Russian Federation remains stable at 110–130 operations per year, which corresponds to the identified need of the population for this method of treatment [1]. In 2020, the Shumakov National Medical Research Center of Transplantology and Artificial Organs (Shumakov Center) performed 98 pediatric liver transplantations, of which 85 were related. Among them, 45 liver transplants were performed for cirrhosis as a result of biliary atresia. The Shumakov Center has reported that one- and three-year liver transplant survival rates are 92.1% and 90.9%, respectively [2].

Survival and long-term outcomes continue to improve for most children receiving related liver transplantation. This is due to improvements in surgical technique, perioperative care, and modern immunosuppressive therapy.

Liver cirrhosis, occurring before the age of 1 year, can affect motor and psycho-speech development in children [3]. The persistence time of cirrhosis differs in children with biliary atresia, depending on the palliative stage of Kasai PE. Often complications of cirrhosis (synthetic liver failure, development of portal hypertension, portosystemic shunting) are masked by normal levels of total and direct bilirubin in children who underwent Kasai PE and lead to late diagnosis of decompensated cirrhosis and delayed liver transplantation.

The literature describes developmental disorders in children with cirrhosis as a result of biliary atresia both

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in preparation for liver transplantation [4, 5] and after it [6, 7].

The objective of this study was to determine the chances of developmental delay in children depending on the time of cirrhosis persistence.

MATERIALS AND METHODS

To realize this goal, we recruited a group of children with biliary atresia (N = 83) who were admitted at the Shumakov Center, Moscow. Inclusion criteria were: established diagnosis of biliary atresia and liver transplantation before 12 months of life. Exclusion criteria were concomitant neurological diseases, neurotoxic reactions to immunosuppressants after liver transplantation.

The children were divided into subgroups depending on the palliative stage of Kasai PE. 47 children underwent Kasai PE at the age of 1–3 months of life, and 36 children without a palliative stage underwent related liver transplantation immediately. Table presents the characteristics of children in subgroups.

Comparative analysis showed that in the subgroup of children who underwent Kasai PE, liver cirrhosis persisted for 2.6 months longer before transplantation than in children without Kasai PE (p = 0.011).

All the children were assessed before and 12 months after liver transplantation using the Griffiths Psychomotor Development Scale (translation and adaptation by E.S. Keshishian) for children up to 24 months of life.

We carried out a statistical analysis of the odds ratio of developmental delay for children depending on the palliative stage of Kasai PE.

RESULTS

The first measurement was made in preparation for liver transplantation. Thirty-four children showed developmental delay: 14 children without palliative stage and 32 children of the Kasai PE subgroup. The difference in the subgroups was statistically significant (p = 0.0018). Fig. 1 presents the number of children in preparation for liver transplantation with normal and abnormal development depending on the palliative stage of Kasai PE.

We analyzed the presence of developmental delay depending on Kasai PE (Fig. 2).

The odds of developmental delay in preparation for liver transplantation were 3.3 times higher in the subgroup of children who underwent palliative Kasai PE compared to children who did not (95%, CI 1.35–8.31).

The second measurement was performed in children 12 months after liver transplantation. In the group of children without Kasai PE, 6 children (16.7%) had a developmental delay of less than 3 months. In the group of children who underwent palliative Kasai PE, 8 patients

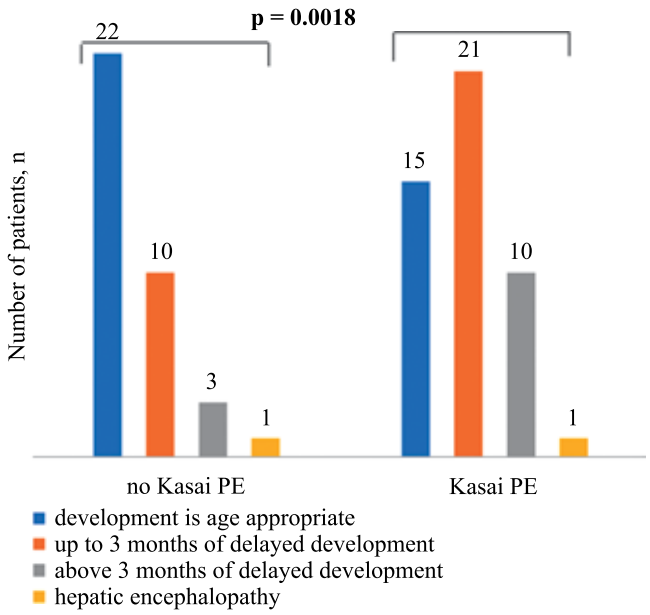

Fig. 1. Developmental levels of children with cirrhosis as a result of biliary atresia at the stage of preparation for transplantation

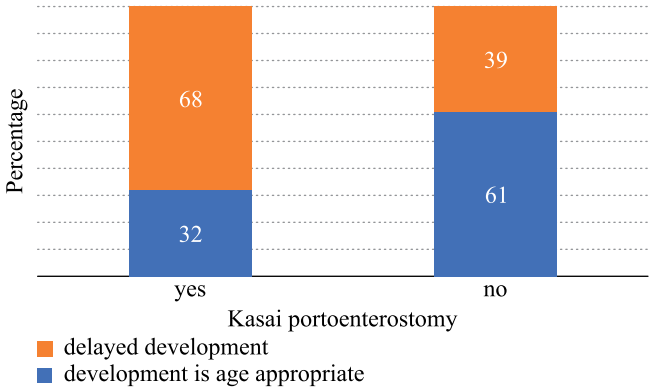

Fig. 2. Analysis of developmental delay depending on palliative Kasai PE

Table

Characteristics of children enrolled in the study

Characteristics	no Kasai PE, n = 36	Kasai PE, n = 47	Significance
Age at liver transplantation, months (min-max)	6.5 (4–15)	9.1 (5–24)	p = 0.011
Number of children with shoulder circumference <3 percentile, n (%)	17 (47)	23 (48)	p = 0.06
PELD mean score (min–max)	23 (13–44)	28.5 (9–34)	p = 0.075
Mean body weight before transplantation, kg (min–max)	6.7 (5.3–9.3)	6.9 (5.0–10.5)	p = 0.34
Hepatic encephalopathy, n (%)	1 (2.8)	1 (2.1)	p = 0.1

showed a developmental delay of more than 3 months, and 14 children had a delay of less than 3 months – a total of 22 children (46.8%). The difference in subgroups with respect to the number of children with developmental delay was statistically significant, p = 0.01 (Fig. 3).

We analyzed the presence of developmental delay in children 12 months after liver transplantation depending on Kasai PE (Fig. 4).

The odds of developmental delay 12 months after liver transplantation were 4.4 times higher in the subgroup of children who underwent Kasai palliative portoenterostomy compared with children without palliative stage (95%, CI 1.54–12.5).

Thus, children with a mean age of 9 months at the time of liver transplantation have a 3.3-fold higher chance of developmental delay before OLTx and 4.4-fold higher chance 12 months after OLTx compared to children who underwent liver transplantation at 6.5 months of age.

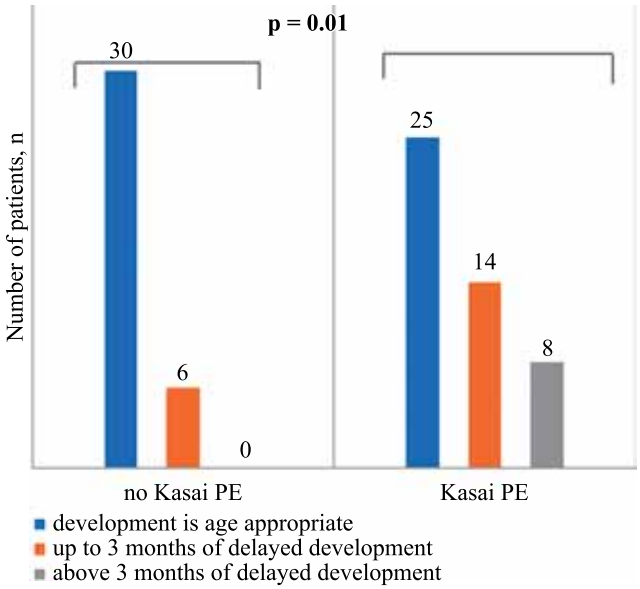

Fig. 3. Developmental levels of children with cirrhosis as a result of biliary atresia 12 months after liver transplantation in subgroups

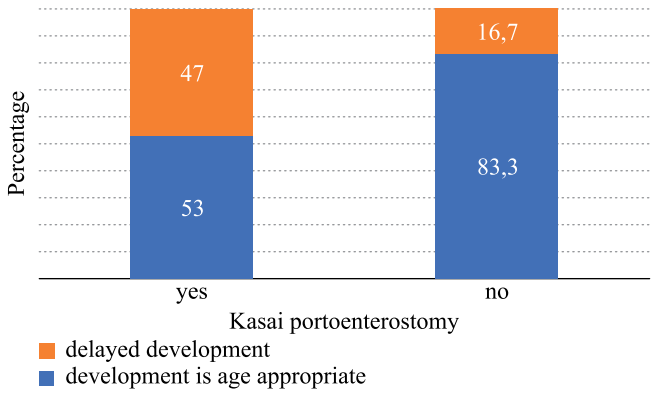

Fig. 4. Analysis of developmental delay depending on palliative Kasai PE

DISCUSSION

The pathogenesis of developmental delay in children with biliary atresia is associated with many processes, such as accumulation of neurotoxic substances affecting the central and peripheral nervous system, catabolic orientation of metabolic processes, insufficient liver synthesis of growth factors, and muscle depletion involved in ammonia detoxification. Increased proinflammatory cytokines IL-6 and IL-18 are shown in patients with cirrhosis [8]. Systemic inflammation means the development of neuroinflammation, which can manifest in different ways. At the level of the central nervous system, it manifests as development of acute conditions: seizures and coma, and chronic neurodegeneration, manifested by developmental and behavioral disorders in children [9–13]. Neuroinflammation at the level of the peripheral nervous system manifests as chronic inflammatory demyelinating polyneuropathy [14, 15] with a clinical picture of muscle weakness, decreased muscle tone and strength, autonomic disorders in patients with biliary cirrhosis [15].

The significance of neuroinflammation is currently being actively studied in the context of various diseases. Whereas, for biliary atresia and decompensated cirrhosis in children, research is required.

Neuroinflammation correlates with cognitive and emotional problems in adults with cirrhosis; in particular, increased levels of tumor necrosis factor alpha are associated with depression and fatigue in chronic liver disease [16]. At the same time, clinical studies devoted to the development of paediatric liver recipients have reported contradictory data. Only some researchers tend to connect developmental disorders of paediatric liver recipients with unsuccessful Kasai PE [17–19].

CONCLUSION

Our study has shown a difference in the developmental level of children with biliary atresia depending on the cirrhosis persistence time. A 2.6-month increase in cirrhosis persistence time increased the odds of developmental delay 3.3-fold before OLTx (95%, CI 1.35–8.31) and 4.4-fold 12 months after OLTx (95%, CI 1.54–12.5). Children who underwent liver transplantation after palliative surgical treatment had lower levels of psychomotor and cognitive development than children without palliative Kasai portoenterostomy both before and 12 months after liver transplantation (p = 0.0018, p = 0.01, respectively).

The authors declare no conflict of interest.

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