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NEUROPSYCHOLOGICAL DEVELOPMENT OF CHILDREN WITH BILIARY ATRESIA AFTER LIVER TRANSPLANTATION

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Background. In young children, the most common liver disease leading to transplantation is biliary atresia. Liver transplantation has fundamentally improved the survival rate of children with biliary atresia. Studies on developmental outcomes in children are mostly limited to small samples; there are no such studies in the Russian Federation. **Objective:** to determine the cognitive outcomes in children undergoing one-stage or two-stage surgical treatment of biliary atresia. **Materials and Methods.** 83 children were divided into groups: 36 children underwent transplantation without previous surgical interventions (group 1), 47 children underwent the Kasai palliative portoenterostomy (group 2). Inclusion criteria: 24 months of age or younger at the moment of transplantation, no medical history of neurological pathology. All children were examined before transplantation and at 1, 3, 6 and 12 months after liver transplantation. Psychomotor development was assessed using the Griffiths Psychomotor Development Scale for children under 24 months (translated by E.S. Keshishian), the Griffiths Intellectual Development Scale for children aged 2 to 8 years, and the Modified Checklist for Autism in Toddlers, Revised, for children 16-30 months old. **Results.** All children had developmental delays at the time of transplantation. Up to 50% of the children had signs of cachexia, with a shoulder circumference of less than 3 percentile. Only two children showed obvious hepatic encephalopathy in the form of depressed consciousness. After liver transplantation, 94% of group 1 children recovered their preoperative psychomotor development levels, and only 68% in group 2 made these gains. At 3 and 6 months after transplantation, about 80% of group 1 children showed normal psychomotor development, whereas in group 2, only 61% did. By 12 months after liver transplantation, the difference between the groups was more evident: 83.3% of group 1 children and only 53.2% of group 2 children were developing according to age. The difference between the groups was statistically significant ($p < 0.05$). **Conclusion.** Children who received one-stage treatment of biliary atresia and underwent liver transplantation have better neuropsychological development within a year after surgery than children with two-stage surgical treatment.

Keywords: liver transplantation, biliary atresia, Kasai portoenterostomy, neuropsychological development, cognitive development.

Over the past decades, liver transplantation has become the gold standard treatment for end-stage liver disease in pediatric patients [1]. Among the indications for liver transplantation, biliary atresia is the most common in childhood [2] [1]. Before surgical treatment, the life expectancy of children with biliary atresia did not exceed 2 years [3]. According to Russian sources, the 1-year and 5-year survival of children with native liver after portoenterostomy is 82.7% and 42.1%, respectively [4]. This is consistent with evidence from Marie-Odile Serinet 2009 about the 5-year survival rate of children after Kasai surgery – 37.9% [3].

The first liver transplantation for biliary atresia in a 3-year-old child was performed in 1953 by the pioneer of orthotopic human liver transplantation Thomas E. Starzl [5]. This event fundamentally changed the survival rate of children with biliary atresia.

Children with biliary atresia develop biliary cirrhosis in the first year of life, during active myelination of the conductive pathways of the central nervous system, which is associated with the risks of impaired psychomotor development. Existing complications of cirrhosis, such as portal hypertension, hepatic cell failure, and hepatic encephalopathy (HE) promote impaired neuropsychiatric development in children. Survival rates are improving every year, whereas there is little information about child development and cognitive outcomes. Studies are conducted on small samples, for which it is difficult to judge objectively development prognosis. There are no such studies in the Russian Federation.

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MATERIALS AND METHODS

The study involved 94 children with biliary atresia operated on at Shumakov National Medical Research Center of Transplantology and Artificial Organs from January 2019 to May 2020. Of these children, 87 met the inclusion criteria – under 2 years of age at the time of related orthotopic liver transplantation (ROLTx), and an unburdened neurological history.

Five children older than 2 years and two children with spontaneous intracerebral hemorrhage in the preoperative period were excluded from the study. See Table 1.

Four patients died during the observation period, which was 4.16% of the total number of children in the study. Among the causes of death were multiple organ failure syndrome in 3 cases and infectious toxic shock syndrome in 1 case.

Thus, 83 children completed the study, including 36 children transplanted without prior surgery and 47 children who underwent palliative Kasai portoenterostomy at the age of 1–3 months. The distribution of children by groups is presented in Table 2.

The level of neuropsychological development was assessed in all children before surgery and 1, 3, 6 and 12 months after liver transplantation. The following scales were used for assessment: the Griffiths Scale of Psychomotor Development (translated by Keshishian E.S.) for children under 24 months [6], the Griffith Mental Development Scale (GMDS) from 2 to 8 years [7], and the Modified Autism Test for Children, Revised (M-CHAT-R, 2009 D. Robins, D. Fein, M. Barton, Russian translation: A. Steinberg, I. Shpitsberg) for children 16–30 months [8].

In accordance with the Griffiths scales, five subscales were scored: "motor skills", "social adaptation", "hearing and speech", "eyes and hands", and "ability to play". Each of the subscales was assigned a certain number of scores according to the level of development of a particular area. The sum of the scores from the five subscales reflected the child's overall development at the time of assessment. The level of development could be both age-appropriate and have abnormalities. For objective comparison of the degree of neuropsychological development of children of different ages deviating from the norm, we identified three categories: general developmental level corresponds to age, development is delayed within 3 months of the norm, development is delayed by more than 3 months of the norm. In further assessments of development at 1, 3, 6, and 12 months after ROLTx, we also used these categories to form statistical data sets.

The Modified Test for Autism in Children, Revised (M-CHAT-R) was administered to all children 16–30 months of age, according to test guidelines. Using a scoring algorithm, a final score was given, corresponding to a child's low, medium, or high risk for autism spectrum disorders.

Table 1

Children with biliary atresia who had intracerebral hemorrhage before liver transplantation

	Patient 1	Patient 2
Age of hemorrhage	3 months	4 months
Type of hemorrhage	Nontraumatic intracerebral hemispheric	Traumatic intracerebral hemispheric, brain contusion, linear fracture of the left parietal bone
Treatment	Surgical	Surgical
Consequences	Spastic hemiparesis, structural epilepsy, psychomotor retardation	Spastic hemiparesis
Age at OLT	9 months	Psychomotor retardation
Anticonvulsants at OLT	Yes	6 months
OLT complications	No	Yes

Table 2

Characteristics of patients in group 1 (no palliative Kasai portoenterostomy) and in group 2 (with palliative Kasai portoenterostomy)

	Group 1	Group 2
Total	36	47
Male	20	27
Female	16	20
Mean age at surgery	6.5 months	9.1 months
Number of children with shoulder circumference <3 percentile	17 (47%)	23 (48%)
PELD (mean)	23	28.5
Preoperative average developmental level	Development delay of 1–3 months	Development delay of >3 months
Hepatic encephalopathy	1	1

Statistical analysis using nonparametric data processing methods, such as Pearson's goodness-of-fit test (chi-square) and correlation coefficient was performed using the STATISTICA 12 program.

RESULTS

All children, regardless of undergoing palliative portoenterostomy, had developmental delays at the preoperative stage of liver transplantation due to the severity of biliary cirrhosis and its complications. Before surgery, the children were underweight and had critically low shoulder circumference. Almost half of the children in each group showed decreased shoulder circumference length below the 3rd percentile, suggesting cachexia and sarcopenia. Only two children showed signs of apparent HE in the form of depressed consciousness.

After related orthotopic liver transplantation, the first assessment of psychomotor development was performed 1 month after surgery. Most children, 94% from group 1, recovered their preoperative developmental level within 2–4 weeks, whereas only 68% of children from group 2 recovered their preoperative developmental level. The level of postoperative complications was higher in the group of children who underwent palliative Kasai portoenterostomy surgery. However, this did not statistically affect the developmental outcomes of children 1 month after liver transplantation ($p < 0.05$).

Three months after liver transplantation, the increase, first of all, in motor skills was evaluated. In group 1, there was a rapid increase in children's motor skills, 80.5% of them demonstrated normal development. In group 2, only 61% achieved normal development.

Six months after transplantation, children in both groups had a slowdown in the rate of skill gain. Group 2 children showed no improvement in development, the same 61% of children fell within the normal intervals of motor and psycho speech development. In Group 1, 88.9% of the children corresponded to their age developmental rates.

At 12 months after liver transplantation, differences between the groups increased significantly. Group 1 children were confidently gaining motor and psychoretic skills, and 83.3% demonstrated normal development. Whereas Group 2 children lagged behind their peers in almost half of the cases. Only 53.2% of the children were assessed within the developmental age range.

At 12 months after liver transplantation in group 1, 6 children (16.7%) had a less than 3 months developmental delay, of which 1 child showed psycho-speech developmental delay without signs of autism, 2 children had signs of autism (scores 4 and 9 on the M-CHAT-R scale, medium and high risk, respectively), and 1 child showed non-autistic developmental regression, the remaining children had delayed speech development.

In group 2, 8 children demonstrated developmental delays of more than 3 months and 14 children had delays less than 3 months – a total of 22 children (46.8%). Of these, 7 children (14.9%) had intermediate or high risk of autism on the M-CHAT-R scale, 4 children (8.5%) had low risk of autism spectrum disorders (less than a score of 2 on the M-CHAT scale), the remaining 11 children (23.4%) exhibited different degrees of speech impairment: from delayed speech development to underdeveloped speech. Figs. 1 and 2 show the dynamics of children's development in Group 1 and Group 2, respectively.

In group 2, the number of children with developmental disorders was statistically significant compared to group 1 children who had better cognitive outcomes ($p < 0.05$).

DISCUSSION

Most studies on the cognitive status of children with biliary atresia, survivors of Kasai portoenterostomy, sug-

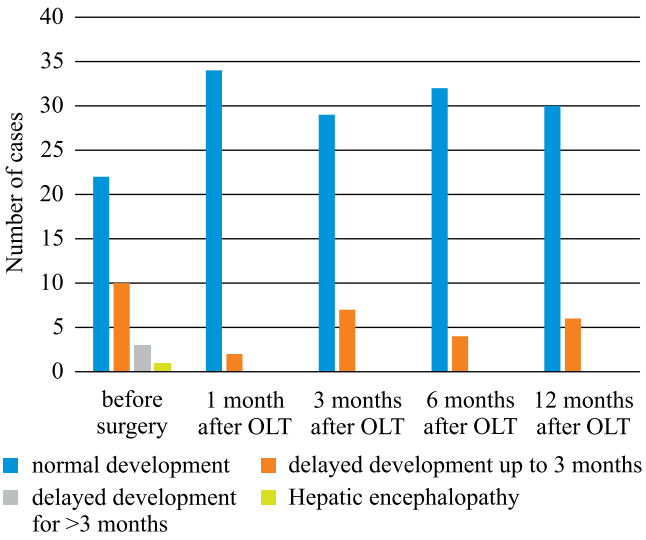

Fig. 1. Development of children, group 1

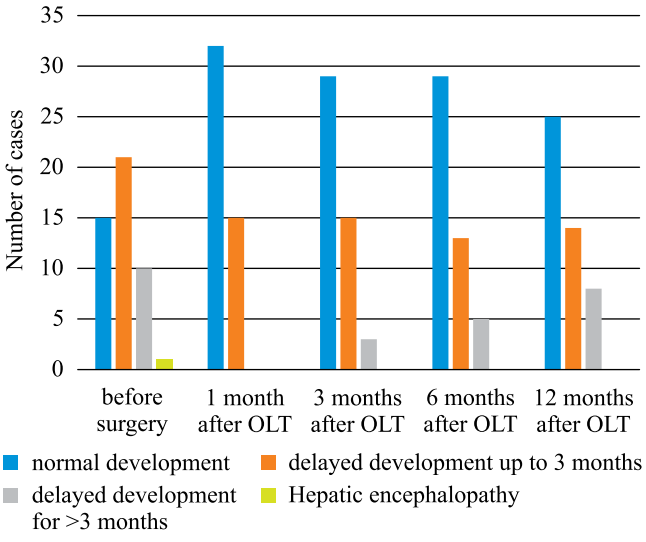

Fig. 2. Development of children, group 2

gest the existing problem of developmental disorders. At different times, the following have been claimed to be predictors of developmental disorders: duration of disease, vitamin E deficiency, protein-energy deficiency [9] [10], serum albumin and bilirubin [11], height and shoulder circumference [12]. None of the predictors have proven to be superior.

Children with biliary atresia who survived with a native liver after hepatoportoenterostomy, in the Squires et al. 2020 study involving 148 children, were at increased risk of neurodevelopmental delay at 12 and 24 months of age. Ascites was a significant predictor of developmental delay. Patients with failed portoenterostomy were more than 4 times more likely to have neuropsychiatric developmental delays than patients with successful portoenterostomy [13]. Portal hypertension was a predictor of decreased IQ in children 3–12 years old with biliary atresia who survived with a native liver. In addition, being male and having high gamma-glutamyl transferase (GGT) levels were predictors of reduced IQ on Wechsler and Wechsler-III tests [13].

Mental disorders play a major role among the consequences for children who have undergone surgical treatment for bilateral atresia. Attention deficit hyperactivity disorder in 31% [14], moderate and severe decrease in IQ 71–85 and IQ <70 in 26% and 4%, respectively [15], developmental disorders associated with sensorineural hearing loss in 5% [16], learning disability in 17%, which is almost 3 times higher than in the general population [10]. The disadvantage of such studies was the small sample size – less than 30 participants.

The spectrum of causes of mental disorders among children with biliary atresia is diverse. HE, which obviously affects the cognitive abilities of patients, is rarely seen in young children. The criteria for diagnosis are blurred in this category of patients. Whereas other causes of developmental delay come to the fore: sarcopenia, anorexia, insulin-like growth factor 1 (IGF-1) deficiency, increased proinflammatory markers and cytokines.

Malnutrition and growth insufficiency before liver transplantation are important risk factors for delayed cognitive development [10].

The brain neurotrophic factor gene is expressed in muscles, adipose tissue, and in the ventromedial nucleus of the hypothalamus and ventral tegmental region. In the brain, a brain-derived neurotrophic factor is responsible for eating behavior and adequate control of food intake. In children with liver cirrhosis resulting from biliary atresia, Wilasco et al. 2016 showed an anorexigenic effect of decreased concentration of brain neurotrophic factor [17].

IGF-1 is synthesized mainly in the liver under the influence of growth hormone. IGF-1 takes a central place in regulation of anabolic processes in the body throughout life. The blood-brain barrier is permeable to IGF1, and peripheral IGF1 enters the brain, where it binds to the receptor via a tyrosine kinase intermediate, triggering the metabolic cascade [18]. IGF1 in in vitro and in vivo studies demonstrates the effects of neuronal dendrite growth and branching, induces apoptosis [19] [20], increases glucose uptake by neurons [21], and determines postnatal neurogenesis and myelination. IGF-1 production in the liver is reduced in the background of cirrhosis [22], while the levels of pituitary somatotropic hormone in the population of children with cirrhosis were high in studies [10].

In patients with cirrhosis, HE is a manifestation of decompensation, along with bleeding from dilated esophageal veins or ascites [23]. HE pathogenesis is currently not entirely clear. It is suggested that HE development is associated with ammonia accumulation, increased circulating and tissue concentrations of tissue glutamine, which leads to cytotoxic cerebral edema and imbalance in the excitatory and inhibitory neurotransmitter systems of the brain [24] [25].

CONCLUSION

Palliative Kasai portoenterostomy performed prior to liver transplantation, negatively affects cognitive outcomes. Children who have undergone two-stage treatment need early intervention programs to correct cognitive, communication, and speech impairments. Children who received single-stage treatment for biliary atresia have better neuropsychiatric development within a year following liver transplantation.

The authors declare no conflict of interest.

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