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PEDIATRIC END STAGE LIVER DISEASES IN KAZAKHSTAN: THE NEED FOR LIVER TRANSPLANT DEVELOPMENT

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The burden of pediatric liver diseases in our country and overall in most of developing countries is poorly studied and less reported. To estimate the number of pediatric end stage liver diseases (PELD) needed a curable transplant is hard to judge with an absence of reliable data. Also, Hepatoblastoma is among one of the common pediatric liver tumors that would need attention for considering liver transplant.

***Aim.** This analysis with a limited number of participants is intended to show the importance of developing liver transplant service in managing end stage pediatric liver diseases. Also, small data regarding Hepatoblastomas in pediatric liver diseases to demonstrate the implementation of liver transplant as a treatment option in multifocal non-resectable Hepatoblastomas.*

***Material and methods.** Retrospective analysis of data with pediatric liver transplant and Hepatoblastoma from UMC, National Research Center for Maternity and Child was analyzed. Considering the small number of participants no statistical methods have been applied.*

***Results and discussion.** The main indication for pediatric liver transplantation was biliary atresia with/without Kasai procedure prior to surgery. HLA typing within close family members is not necessary. Pediatric patients with unresectable Hepatoblastoma would benefit from referring to Transplant consideration on timely manner.*

***Conclusion.** Liver transplantation is the only viable option for pediatric end stage liver diseases. The main etiology among pediatric cases in compliance with worldwide data is biliary atresia as our results presented. From this small analysis we aspire to advance our transplant service by considering liver transplantation in multifocal nonresectable hepatoblastoma cases. Nonetheless, HLA matching in close relatives has shown to be not necessary to focus in liver transplantation its role is important in further control of donor specific antibodies in case of rejection occurrence.*

***Key words:** pediatric liver diseases, liver transplantation, hepatoblastoma.*

For end stage liver disease among pediatric population aged less than 2 years old there is no accurate scoring system available to allocate for the need for transplantation [1]. The absence of unified wait list system to manage this pediatric cases challenges to estimate the number needed a transplant service. The approximation from the last update was more than 20 children with various congenital or acquired liver pathologies are awaiting for liver transplantation. In confirmation with the worldwide data among Kazakhstani cases Biliary atresia is the leading cause in PELD for liver transplant in children, especially in patients at early years of life [2]. Some US studies recently reported the increase in incidence of this tumor from 0.6 to 1.2 per million [3]. According to Browne M. et.al. Liver transplantation is a successful treatment option for children with unresectable hepatoblastoma with a 90% survival rate for primary transplantation. Among pediatric oncology cases in Kazakhstan hepatoblastoma has similar incidence with the worldwide data.

MATERIAL AND METHODS

During the period from 2012 to 2015 at UMC, National Research Center for Maternity and Child in Astana, there are total of 6 pediatric living donor liver transplantations were performed. Also, total of 7 hepatoblastoma cases since 2012 from this hospital included in this analysis to visualize the possible role of considering liver transplantation in this category of patients.

RESULTS

In all cases of performed liver transplantation, the left lateral segment of the donor liver was allocated for transplantation. Age of recipients ranged from 5 months up to 6 year old. The donors are close relatives of the recipient, with 4 of them performed HLA compatability analysis as shown in Table-1, their age ranged from 24 to 36 years (Table - 1). Major 3 heterodimers: HLA-A, -B, and -DRB1 which contributes to immunogenicity of mismatched antigens, they were analyzed in 4 pairs of donor-recipients at the initial stages. Even though, the role of HLA typing in liver transplantation is still uncertain, but could be beneficial in long-term graft survival analysis.

Table 1 – **HLA compatibility of 4 pairs**

Recipient				Donor			
A	B	DRB1	DRB	A	B	DRB1	DRB
02;26	15;51	04;14	3;4	26*29	07*51	10*14	3*-
01;02	08;15	03;07	3;4	02*-	15;27	01;07	4;-
24*31	15*35	04*11	3*4	01*03	07*35	01*15	5* -
01*02	08*27	01*11	3*-	02*-	27*40	01*04	4*-

In 4 out of 6 cases in children under the age of 1 year old the etiology of liver cirrhosis was biliary atresia. In 2 of them Kasai procedure was performed prior to considering liver transplant

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surgery. In a 6 y.o. child the underlying cause of cirrhosis was autoimmune hepatitis. Another child had a possible CMV virus induced secondary cholestatic cirrhosis (Table-1). PELD scores were not calculated since for children under age of 2 in recent years losing its accuracy in predicting survival.

All liver transplant surgeries carried out with the participation of foreign experts from India, Turkey, and The Republic of Belarus. Postoperative complications were not observed in donors. One child under the age of 5 months had a PO-complication as hepatic artery thrombosis (HAT). The surgical actions to fix the vascular damage were unsuccessful and the child was taken by sanitary aviation to hospital in Istanbul, Turkey, where he had another living donor liver transplant. In the remaining five recipients there were no complications observed, and they are discharged from the hospital with good follow-up results.

Table 2 — **Pediatric liver transplant characteristics**

Recipient characteristics (n=6)	Age 0 – 2 y.o.	Age 2 – 6 y.o.
Total numbers	5	1
Biliary atresia Kasai procedure (<3 m.o)	4 2	0 0
Viral etiology (CMV)	1	0
Autoimmune hepatitis	0	1
Complications:HAT	1	0

Another important aspect of this study was to look at hepatoblastoma cases whether there was a possibility of considering pediatric liver transplant in patients with unresectable hepatoblastomas. In order to identify this we intended to look at 7 cases of hepatoblastoma treated at UMC, National Research Center for Maternity and Child in Astana from 2012. Due to the small number of patients no statistical data was calculated other than mean values. Mean age at time of diagnosis was 5 y.o. Male to female ratio was 5:2. Staging of hepatoblastoma in all cases was PRETEXT III-IV, SIOPEL 4 with high risk group, with/without metastasis. Morphology of the tumor was represented as embryonic type or epithelial mesenchymal type with high AFP values (mean AFP = 45960 IU/ml). Mean LDG was 382 IU/ml. Two patients had liver resection with prior/post administration of chemotherapy according to Vorschlag zu Therapiestrategie beim SR Hepatoblastom Protocol with decrease of AFP in dynamics (to mean of 1850 IU/ml). The follow-up results after surgery/chemotherapy hasn't detected any recurrent tumors.

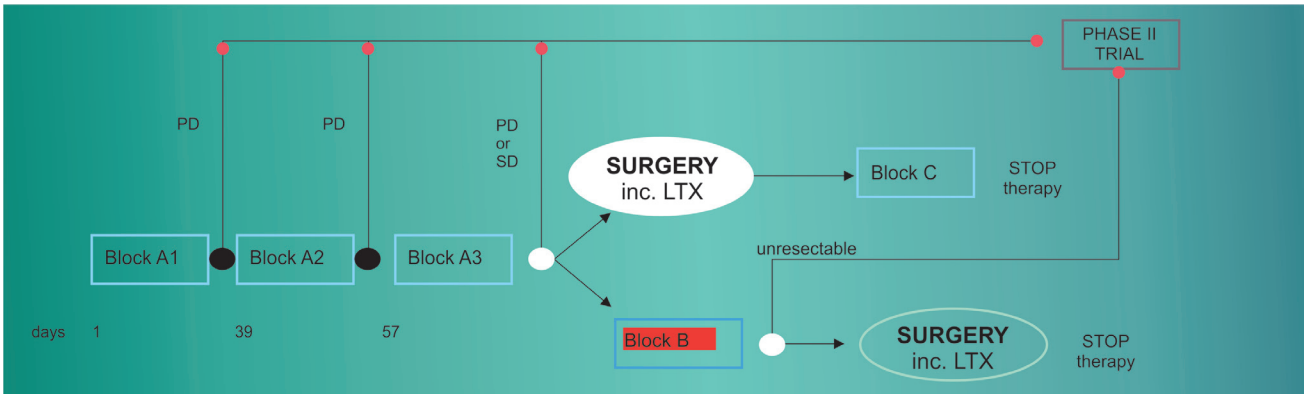
One 1 y.o. patient had lung and distant lymph node metastasis at the time of diagnosis and died of complications after 5 days in pediatric ICU department. Another 15 y.o. patient with SIOPEL-PRETEXT IV with multifocal hepatoblastoma, histologically proven to be epithelial-mesenchymal type was a strong candidate for liver transplantation with no metastatic involvement and positive dynamics of tumor shrinking/and AFP decrease after 3 blocks of therapy. Due to time delay of sending abroad for liver transplant surgery on later courses this patient developed distance metastasis and continued on chemotherapy per protocol and following up in block B category as shown in this schematic image-1.

DISCUSSION

The only viable option for end stage pediatric liver diseases is liver transplantation. Kazakhstan implemented "Organ Transplant Law" starting from 2011, but we haven't been able to develop split liver transplant from cadaveric donors to increase the pool for pediatric cases. It leaves us with an option to concentrate on living donor liver transplantation development for children with PELD. Due to the lack of experience among local transplant surgeons in carrying out highly advanced surgeries in young children, most patients consider liver transplant in foreign clinics by governmental funding or on their own expenses. Thus, there is a high necessity in increasing the training and hands on experience of pediatric liver surgeons in advancing their techniques and knowledge in this area. Another question that has to be addressed in the future is the possibility of offering living donor liver transplants in a timely manner for patients with unresectable hepatoblastoma as a viable option with a 90% of survival rate for primary transplantation considering an adequate chemotherapy [4]. It is still a controversial whether to perform this surgery and in most of the cases this tumor progresses abruptly. As shown from our small data with one example of multifocal unresectable hepatoblastoma with successful chemotherapy courses, that patient would have benefited from liver transplant early on time before the progression of the disease. With the availability of diagnostic tools for metabolic liver conditions, congenital disorders, and increasing numbers of fulminant liver failure, as well as end stage cirrhosis among pediatric population we need to pay special attention into putting a vast majority of intellectual and financial resources into this problem in Kazakhstan.

CONCLUSION

Liver transplantation is the only viable option for pediatric end stage liver diseases. The main etiology among pediatric cases in compliance with worldwide data is biliary atresia as our



Picture 1 - A Multifocal unresectable Hepatoblastoma case

results presented. From this small analysis we aspire to advance our transplant service by considering liver transplantation in multifocal nonresectable hepatoblastoma cases. Nonetheless, HLA matching in close relatives has shown to be not necessary to focus in liver transplantation its role is important in further control of donor specific antibodies in case of rejection occurrence.

Research transparency

Research did not have a sponsorship. The authors are absolutely responsible for presenting the release script for publication.

Declaration about financial and other relations

All authors took part in elaboration of article conception and writing the script. The release script was approved by all authors. The authors did not get the honorary for the article.

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ТҰЖЫРЫМ

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Педиатриялық бауыр ауруларының таралуы бойынша статистикалық мәліметтердің және жалпы тіркеу критерияларының болмауы бауыр трансплантациясын қажет ететін баланы операцияға дайындау мен нәтижелі емшараны ұйымдастыруды қиындатады. Сонымен қатар, балалар арасында кең таралған бауыр қатерлі ісігі гепатобластоманың мультифокальды резекция жасалмайтын жағдайында бауыр трансплантациясының рөлін қарастыру мүмкіндігін талқылау.

Зерттеудің мақсаты. Балалар арасында бауырдың декомпенсация дамуы жағдайында жасалған трансплантация бойынша тұжырым жасау. Сонымен қатар, гепатобластомаға шалдыққан балалар арасында қай жағдайда уақытында бауыр трансплантациясын қарастыру қажет екенін көрсету.

Материал және әдістері. UMC Корпоративтік қоры, Ұлттық Ана мен Бала Орталығында бауыр трансплантациясы мен гепатобластома бойынша ретроспективті талдау жүргізу. Талдауға қосылған балалар санының шектеулігіне байланысты статистикалық есеп жүргізілмеді.

Нәтижелері және талқылауы. Бауыр трансплантациясына негізгі көрсеткіш Касаи процедурасынан кейінгі немесе оның қолдануынсыз өт жолдарының атрезиясы. HLA талдауы бойынша жақын бауырлар арасында өткізудің қажеттігі жоқ, тек трансплантациядан соң иммундық жауапты талдауға қажеттілік болмаса. Резекция жасауға келмейтін гепатобластома кезінде дер кезінде трансплантация қарастыру науқас өмірін ұзартуға септігін тигізу ықтималдығы жоғары.

Қорытынды. Педиатриялық бауыр декомпенсациялық ауруларында бауыр трансплантациясы негізгі емдеу тәсілі болып табылады. Резекция жасалмайтын мультифокалды гепатобластома кезінде трансплантация ем тәсілі ретінде қолданылады.

Негізгі сөздер: *педиатриялық бауыр аурулары, бауыр трансплантациясы, гепатобластома.*

РЕЗЮМЕ

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Распространенность заболеваний печени среди детей в нашей стране и в целом в большинстве развивающихся стран плохо изучено и менее известно. Отсутствие надежных данных по заболеваемости влияет на прогноз и предварительную подготовку пациентов на трансплантацию печени. Одни из частых образований печени среди детей гепатобластомы требуют внимания при нерезицируемых формах для своевременного рассмотрения трансплантации печени.

Цель данного анализа – показать важность развития службы трансплантации печени при лечении педиатрических заболеваний печени. А также среди пролеченных случаев гепатобластом выявить случаи мультифокальных поражений печени, при которых пересадка печени была бы целесообразным решением.

Материал и методы. Ретроспективный анализ данных педиатрической трансплантации печени и гепатобластом в UMC, Национального Исследовательского Центра материнства и детства. Учитывая небольшое количество участников, статистические методы не применялись.

Результаты и обсуждение. Основным показанием педиатрической трансплантации печени была атрезия желчных путей с проведением либо без процедуры Касаи. По данным HLA типирования необходимости в проведении дорогостоящего анализа нет, если только не стоит вопрос о выживаемости графта в отдаленном периоде. Педиатрическим пациентам с неоперабельной гепатобластомой было бы полезно своевременно обратиться к вопросу рассмотрения трансплантации печени.

Выводы. Трансплантация печени является единственным методом лечения при декомпенсированных заболеваниях печени у детей. А также она может стать методом лечения при нерезецируемых мультифокальных гепатобластомах.

Ключевые слова: *педиатрические заболевания печени, трансплантация печени, гепатобластома.*

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