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DE NOVO AUTOIMMUNE HEPATITIS AFTER LIVER TRANSPLANTATION IN CHILDREN. REVIEW

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Conflict of interest
The authors declare that they have no conflicts of interest

Abstract

De novo autoimmune hepatitis (AIH) is a clinical disease similar to AIH that develops in liver transplant recipients with diseases other than AIH. Timely recognition of this disease makes it possible to avoid graft rejection and liver re-transplantation (LT), liver fibrosis, and can ensure a long life expectancy, given the effectiveness of more active immunosuppression with the use of corticosteroids and azathioprine, as in the treatment of idiopathic AIH. The de novo prefix was added to distinguish this condition from primary autoimmune hepatitis prior to transplant, but the diagnostic algorithm adopted generally accepted diagnostic criteria for autoimmune hepatitis. In fact, de novo autoimmune hepatitis is characterized by typical necroinflammation of the liver, rich in plasma cells, increased serum gammaglobulin levels, and the appearance of inorganic specific autoantibodies. However, the general signs of autoimmune hepatitis de novo, apparently, cannot be associated with an unambiguous pathophysiological pathway, since they can develop in patients undergoing liver transplantation due to different etiologies.

The literature review presents such aspects as the prevalence of this case, the influence of the HLA phenotype on the manifestation and outcome of the disease, diagnosis and treatment.

Objective. *To conduct a literary review of scientific publications on the development of De novo Autoimmune hepatitis after liver transplantation in children.*

Materials and methods. *The authors selected scientific bases for the search such as: Web of science, Cyberleninka, UpToDate, Pubmed and Cochrane, Google Scholar.*

Results. *A meta-analysis of scientific articles in English and Russian was carried out for the selected keywords. The causes of development were not infectious or surgical complications. Liver biopsy revealed histological changes typical of acute or chronic ovulation. High levels of transaminases, hypergammaglobulinemia, positivity to autoantibodies – ANA, AMA, SMA, anti-LKM-1. De novo AIH patients did not respond to conventional anti-rejection therapy, but responded only to classical AIH therapy.*

Keywords
schoolchildren, valvular regurgitations, prevalence

Балалардағы бауыр трансплантациясынан кейінгі de nova аутоиммунды гепатиті. Әдебиет шолуы

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Аңдатпа

De novo аутоиммунды гепатит (АИГ) – АИГ-ға ұқсас клиникалық ауру, басқа аурулардың нәтижесінде өткерілген бауыр трансплантациясынан кейін дамиды. Бұл ауруды дер кезінде анықтау арқылы трансплантатты қабылдамау, қайта трансплантация, бауыр фиброзы сияқты салдарлардың алдын алуға болады, сонымен қоса, кортикостероидтар мен азатиопринмен активті иммуносупрессияны қолданып, өмір сүру уақытының ұзақтығын қамтамасыз етеді.

De novo қосымшасы бұл жағдайды трансплантацияға дейінгі біріншілік аутоиммунды гепатиттен ажырату үшін қосылған, алайда диагностикалық алгоритмде аутоиммунды гепатитті анықтаудың жалпы өлшемдері қолданылады. Негізінде De novo аутоиммунды гепатит бауырдың плазмалық жасушаларына бай типтік некроқабынуымен, қан сарысуында гаммаглобулин деңгейінің жоғарылауымен, органикалық емес спецификалық аутоантиденелердің пайда болуымен сипатталады. Бірақ De novo аутоиммунды гепатиттің жалпы белгілері бір патофизилогиялық жолмен байланыспайды, себебі бауыр трансплантациясы әртүрлі этиологияға байланысты жасалынады.

Әдебиеттік шолуда осы жағдайдың таралуы, HLA фенотипінің аурудың дамуы мен асқынуына әсері, диагностикасы және емі баяндалады.

Жұмыстың мақсаты *- балалардағы бауыр трансплантациясынан кейінгі De novo аутоиммунды гепатиттің дамуы жайлы ғылыми басылымдарға әдебиеттік шолу жасау.*

Материал және әдістер. *Іздеу үшін мына ғылыми базалар таңдалынды: Web of science, Cyberleninka, UpToDate, Pubmed и Cochrane, Google Scholar.*

Нәтижелер. *Таңдалған түйін сөздер бойынша орыс және ағылшын тілдерінде ғылыми басылымдардың мета-анализі жүргізілді. Аурудың дамуы инфекция немесе хирургиялық асқынудан болмаған. Бауырдың биопсиясы кезінде трансаминазалардың жоғары деңгейі, гипергаммаглобулинемия, аутоантиденелерге позитивтілік – ANA, AMA, SMA, anti-LKM-1 анықталды. De novo АИГ-мен ауыратын науқастар тек АИГ-ның классикалық еміне жауап қайтарды.*

Түйін сөздер
аутоиммунды гепатит, бауыр трансплантациясы, педиатриялық трансплантация, de novo гепатит, бауыр циррозы

Denova аутоиммунный гепатит после трансплантации печени у детей. Обзор литературы

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Аннотация

De novo аутоиммунный гепатит (АИГ) - это клиническое заболевание, напоминающее АИГ, которое развивается у реципиентов после трансплантации печени при других заболеваниях, кроме АИГ. Своевременное распознавание данного заболевания позволяет избежать отторжения трансплантата и повторной трансплантации печени (ТП),фиброза печени, и может обеспечить высокую продолжительность жизни, учитывая эффективность более активной иммуносупрессии с применением кортикостероидов и азатиоприна, как и при лечении идиопатического АИГ. Приставка denovобыла добавлена для того, чтобы отличить это состояние от первичного аутоиммунного гепатита до трансплантации, но в диагностическом алгоритме были приняты общепринятые критерии диагностики аутоиммунного гепатита. На самом деле, аутоиммунный гепатит de novo характеризуется типичным некровоспалением печени, богатыми плазматическими клетками, повышением уровня гаммаглобулина в сыворотке крови и появлением неорганических специфических аутоантител. Тем не менее, общие признаки аутоиммунного гепатита denovo,не могут быть связаны с однозначным патофизиологическим путем, поскольку они могут развиваться у пациентов, перенесших трансплантацию печени, из-за различной этиологии.

В обзоре литературы представлены такие аспекты, как распространенность данного случая, влияние HLA фенотипа на проявление и исход заболевания, диагностика и лечение.

Цель работы - *провести литературный обзор научных публикаций по развитии De novo аутоиммунного гепатита после трансплантации печени у детей.*

Материалы и методы. *Авторами выбраны научные базы для поиска такие как: Web of science, Cyberleninka, UpToDate, Pubmed и Cochrane, Google Scholar.*

Результаты. *По выбранным ключевым словам был проведен мета-анализ научных статей на английском и русском языках. Причинами развития не были ифекционные или хирургические осложнения. При биопсии печени были выявлены гистологические изменеия типичные для острого или хронического отторжения. Были выявлены высокие уровни трансаминаз, гипергаммаглобулинемия, позитивность к аутоантителам – ANA, AMA, SMA, anti-LKM-1. Пациенты с de novo АИГ не отвечали на обычную терапию против отторжения, а отвечали только на классическое лечение АИГ.*

Ключевые слова
аутоиммунный гепатит, трансплантация печени, педиатрическая трансплантация, de novo гепатит, цирроз печени

Introduction

Liver transplantation (LT) is considered the main therapeutic approach for end-stage acute and chronic liver disease. Approximately 90% of liver transplant patients are alive and well at 1 year and 75% at 5 years, with most living full and near-normal lives. Early post-transplant mortality rates have dropped sharply over the past two decades, while late graft loss and patient death rates have remained unchanged. Therefore, the reasons for graft and patient failure are important to improve future outcomes. In the early days after LT, ischemia and reperfusion injuries predominate, while acute cellular rejection is relatively common in the first 3 months. And after the cause of graft dysfunction may vary, and recurrence of the disease is the main cause of graft loss [1].

Initially, de novo AIH was described predominantly in children with biliary atresia and was later found to be more prevalent in PBC recipients. The first de novo description of AIH was in children in 1998, with 7 of 180 children followed up for at least 5 years after LT. These patients had histological signs of AIH, hypergammaglobulinemia and high titers of ANA, SMA, anti-LKM1. Of these 7 patients, 6 responded to therapy with corticosteroids and azathioprine. Since then, subsequent studies have confirmed the occurrence of de novo AIH in 1-7% of patients aged 0 to 9 years after LT [2].

The age of the recipient may be an important determinant of de novo AIH. Most often occurs and is more severe in children 3]. Miyagawa-Hayashino et al. [4] reported that age 11 to 15 years was an independent prognostic factor for de novo AIH in a large group of LT recipients from living donors.

The incidence of de novo AIH is unknown because there are no systematic diagnostic criteria for this disease. Moreover, the de novo outcome of AIH is unclear, as there are few studies evaluating its effect on graft or patient survival. Female transplant recipients or older donors have a higher prevalence of de novo AIH, indicating that the risk associated with de novo AIH may be dictated by the allograft itself [5].

The 5-year survival rate after LT in AIH is 80-90% [6]. The results of AT with AIH are good, but the disease can recur in the allograft despite immunosuppression. The average time from TP to relapse is 5 years, but relapse can occur as early as 35 days after surgery [7]. The recurrence rate of AIH varies between 30-83% and depends on the diagnosis, treatment, duration of follow-up and the results of

histological examination of liver tissue. The diagnosis of recurrent AIH is based on the appearance of clinical symptoms of hepatitis, increased levels of transaminases and IgG, autoantibodies, response to treatment with corticosteroids and azathioprine. Reasons associated with the recurrence of AIH after LT: histocompatibility antigens HLA-DR3 or HLA-DR4; discontinuation of corticosteroids after LT, severity of necroinflammatory activity in the native liver during LT. Recurrent AIH develops less frequently in patients transplanted for the fulminant course of AIH with ALF compared with patients with a chronic form of the disease [8].

The formation of nonspecific autoantibodies is detected over time after liver transplantation, affecting more than 70% of recipients [9,10], the incidence of de novo AIH in children ranges from 2-6% [11,12]. These pathological changes, which occur in 4% of children transplanted for various liver diseases, were first described at King's College Hospital (London, UK) [13]. The patients developed a form of graft dysfunction characteristic of classical AIH: high transaminase levels, hypergammaglobulinemia, positive autoantibody titers ANA, ASMA, typical and atypical anti-LKM-1, and histological features characteristic of chronic hepatitis with portal or periportal inflammation and centrolobular necrosis.

The pathogenesis of de novo AIH is poorly understood; it is a form of graft intolerance or a special mode of graft rejection that is not directed against HLA molecules. In the case of de novo AIH associated with antibodies against GSTT1, patients with a GSTT1 genotype null who received a transplant from a positive donor can be described as satisfying the basic condition for the development of de novo AIH [14, 15]. However, not every patient with this genetic mismatch will develop clinical signs de novo AIH. The history of immunological and clinical features of patients with GSTT1 mismatch and anti-GSTT1 antibodies after LT has not been described.

De novo AIH has been associated with atypical serum autoantibodies, which are antibodies against glutathione S-transferase T1 (anti-GSTT1). In fact, the discrepancy between the donor and recipient in the GSTT1 genotype is a necessary factor for the emergence of anti-GSTT1 and the de novo development of AIH.

De novo AIH should be distinguished from acute rejection, chronic rejection, viral infection, and drug side effects. Histological features and the time interval between disease onset and liver transplantation are important in guiding diagnostic efforts [16–22]. Acute rejection occurs within 30 days after LT and is characterized by portal and central endothelitis, damage to the bile ducts and eosinophils, and chronic rejection develops 3-12 months after LT and is characterized by cholestatic laboratory findings: bile duct loss. lesion of more than 50% of the portal tracts, loss of a small artery, perivenular fibrosis, and obliterating foam cell arteriopathy [16].

Other causes of graft dysfunction after liver transplantation, such as rejection, infection, and hepatic artery thrombosis, were ruled out. Study patients with De novo AIH did not respond to standard antiretroviral therapy, but responded to classical AIH therapy. None of the children had undergone transplants for autoimmune liver disease, and all had therapeutic antireactive serum calcineurin inhibitor concentrations at the time of de novo AIH diagnosis. De novo AIH is sometimes a complication in liver transplant donors [23]. The largest pediatric trial published to date describes 41 out of 788 patients with single-center TP who developed de novo AIH. Graft rejection and steroid dependence have been identified as risk factors for this complication [24]. In adults, the development of this condition can be predicted using a histological picture characterizing centrilobular inflammation with necroinflammatory activity and plasma cell infiltration. In children, the histological feature of de novo AIH is lobular hepatitis without necroinflammatory activity or plasma cell infiltrates [25].

Several reports investigated the relationship between the de novo development of AIH after liver transplantation with the possession of a specific major histocompatibility complex (MHC) antigen between recipient and donor. In the report, five out of seven patients received livers from donors with HLA alleles known to confer sensitivity to AIH, two being DR4, one DR3 and two being DR3 / DR4, while no association was found to possess DR3 or DR4 recipient [13]. Henegan et al. [26] found HLA DRB * 0301 or DRB * 0401 in donors or recipients in all cases, and Salcedo et al. [27] found an overrepresentation of DR3 in recipients. It is necessary to investigate a larger number of patients to establish the immunogenetic effect on the de novo development of AIH after liver transplantation.

If the five-year survival rate after liver transplantation is 92%, the autoantibodies disappear within two years. Recurrence of autoimmune hepatitis after liver transplantation has been reported in patients who received overdose of immunosuppressive drugs and in HLA DRS-positive patients who received HLA DR3-negative transplants.

Role of liver biopsy for diagnosis and decision making in De Novo autoimmune hepatitis?

According to the Banff Working Group, the histological criteria used to diagnose De novo AIH in a liver allograft are similar to those used to recognize AIH in a nontransplant setting [28]. Many studies have identified a typical plasma cell rich infiltrate showing a significant necroinflammatory interface and perivenular activity [29]. De novo AIH should be differ-

entiated from other causes of hepatitis, such as idiopathic chronic hepatitis after LT and viral hepatitis. In a large cohort of 51 pediatric patients diagnosed with De novo AIH, the predominant histological pattern of damage was necroinflammatory activity, presented as lobular hepatitis, followed by interface and perivenular activity [30]. The rest of the injury patterns were similar to those observed in acute rejection, chronic rejection, and bile duct obstruction. 80% of liver biopsies showed no or moderate fibrosis. An infiltrate rich in plasma cells was observed in only 31% of patients; they affected the portal areas. A decrease in the severity of hepatitis and plasma cell rich infiltrates was indicated in biopsies taken from these patients after treatment with corticosteroids. Sebagh et al. [31] developed a mathematical model to assess the predictability of the histological diagnosis of DAIH. This model had the best level of predictability (99.6%) when both severe centrilobular necroinflammatory activity and a centrilobular plasma cell ratio of 30-50% were present. This model can be useful for separating DAIH from other nosologies [32]. Diagnosing autoimmune hepatitis de novo (AIH) after orthotopic liver transplantation (OLT) is difficult when hypergammaglobulinemia is absent. Circulating autoantibodies are not sensitive or specific for de novo AIH, but a positive result increases the diagnostic likelihood. There is evidence of the discovery of new autoantibodies to liver microsomes against CYP-2C19 in a 9-year-old boy with de novo AIH who developed 7 years after OLT. Graft dysfunction is manifested by hypertransaminasemia, and gammaglobulins were normal. Liver histology and response to high dose corticosteroids supplemented with azathioprine further confirmed the de novo AIH diagnosis. The study of autoantibodies by indirect immunofluorescence in rodent tissues showed a new staining pattern affecting the pericentral zone of the liver and preserving the renal tissue. Immunoblotting of human liver proteins allowed them to characterize new antibodies to liver microsomes and identify CYP-2C19 as a human antigen [33]. De novo AIH can be aggressive in children. In one pediatric group, 80% of recipients had an outcome as pronounced fibrosis, and graft loss occurred in 33%, despite the combined treatment of corticosteroids with azathioprine. Adult patients who develop de novo AIH after treatment for recurrent HCV infection with interferon may also be aggressive. In the first group, 2 out of 9 patients were fatal, and 1 patient had graft rejection and 1 patient required a second transplant, despite the rapid initiation of corticosteroid treatment.

De novo AIH should be distinguished from acute rejection, chronic rejection, viral infection, and drug side effect. The difficulty in making a diagnosis is due to the lack of a specific marker. Recurrent AIH develops in about 20–25% of cases [34,35]. The awareness that treatment with prednisolone and azathioprine is effective for de novo AIH after LT has resulted in excellent graft and patient survival. This is documented in an article describing the experience of a single center for de novo AIH treatment after liver transplantation. The retrospective drug-naive group was compared with the prospective group of patients receiving steroids and azathioprine. While all patients who did not receive drug treatment developed liver cirrhosis and were fatal or required a second transplant, none of the treated patients had progression of the disease within four years. At the stage of drug treatment, an increased dose of corticosteroids or their resumption of administration with or without azathioprine or MMF are used [36]. When we do not see the desired response, azathioprine / MMF can be substituted for sirolimus [37]. The prophylactic use of azathioprine in patients with liver transplants associated with AIH has not been systematically evaluated, although such a tactic seems to be justified. AIH de novo has been described in 2–7% of patients after LT for various diseases not associated with autoimmune processes, especially in children. The treatment strategy is the same as for recurrent AIH. Finally, patients with recurrent or de novo AIH should be considered for re-transplantation if AIH progresses to graft loss (rarely with early treatment) [38].

De novo AIH has been described as a manifestation of immune restoration in HIV-infected patients receiving highly active antiretroviral therapy. Liver biopsy data play an important role in establishing the diagnosis of AIH and differentiating numerous other causes of changes in liver function parameters in these patients [39]. Standard AIH immunosuppressive therapy can be effective, but sometimes it is complicated by the development of life-threatening infections. Treatment of AIH in HIV-infected patients should be individualized and take into account the possible risks and benefits [40].

Conclusion

The de novo position of AIH in the spectrum of allograft dysfunction is still undetermined, and further research is needed to standardize its diagnosis and distinguish it from plasma cell-rich rejection. This requires looking for disease-specific serologic markers and determining the value of anti-GSTT1 testing. In pediatric patients with unexplained graft dysfunction after LT, it is important to quickly recognize de novo AIH and develop an adequate diagnostic strategy, including assessment of serum autoantibodies, immunoglobulin G, and liver biopsy.

Early diagnosis and prompt initiation of therapy with prednisolone or prednisolone in combination with azathioprine are the main principles of treatment of recurrent and de novo autoimmune hepatitis.

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