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A Clinical Case of the Autoimmune Hepatitis Type ii In A Child with Diabetes Mellitus

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Abstract

Autoimmune hepatitis (AIH) is an immuno-mediated inflammatory liver disease of unknown etiology, which does not depend on gender, age, ethnicity, characterized by hypergammaglobulinemia and the presence of anti-LKM1 in blood serum [1].

This article demonstrates the clinical observation of the development of AIH in a patient with type I diabetes mellitus (type I DM). At the age of 8, the child had jaundice syndrome against the background of the underlying disease. Biochemical examination revealed hyperbilirubinemia due to indirect fraction, cholestasis syndrome, and immunological activity of anti-LKM1.

Subsequently, an increase in the titer of antibodies to LKM1 was noted, and therefore the patient was prescribed immunosuppressive therapy. Against the background of the ongoing treatment, it was possible to reduce immunological activity and achieve remission. Despite the necessary and regular treatment, the girl remains hyperglycemic and has a high level of glycated hemoglobin.

Keywords: Children, Type I Diabetes Mellitus, Autoimmune Hepatitis, Insulin Therapy, Cirrhosis

Introduction

Autoimmune hepatitis (AIH) is a T–cell-mediated inflammatory liver disease characterized by an increase in serum aminotransferases and immunoglobulin G (IgG) levels by positive circulating autoantibodies and the presence of intercellular hepatitis during histological examination of the liver [2]. AIH is considered as a relatively rare disease: its prevalence in Europe and the USA is 3-17 cases per 100,000 population, and the annual incidence is 0.1–1.9 cases per 100,000 population [3]. There are 3 types of AIH (however, there are still disputes about the presence of 3 types): Type I AIH – is accompanied by the circulation of antinuclear antibodies (ANA) in 70-80% of patients and/or anti-smooth muscle autoantibodies (SMA) in 50-70%. For this type of AIH, the typical age of manifestation is the period from 10 to 20 and the postmenopausal period. Type II AIH – is characterized by the circulation of antibodies to type 1 liver and kidney microsomes (anti-LKMl), detected in 100% of patients, sometimes in combination with anti-LCM3 and antibodies to he-

patic cytosolic protein (anti-LC1). Type II AIH – is less common (10-15% of patients with AIH) and mainly in children from 2 to 14 years old. Type III AIH – is characterized by the presence of antibodies in the blood to soluble liver antigen (anti-SLA) and hepatic pancreatic antigen (anti-LP).

This pathology is often found in middle-aged patients, in children much less often. The estimated incidence of type II AIH varies worldwide depending on the region and age of onset of the disease, so the prevalence rates among children range from 0.23 (Canada) to 0.4 per 100,000 people (USA). However, over the past few decades, Spain, Denmark, Sweden and the Netherlands have seen an increase in the incidence of almost 50% [2-5]. In Russia, the proportion of AIH in the structure of chronic hepatitis in children is 2.0%. Genetic predisposition is considered as the main factor in the pathogenesis of AIH. AIH is characterized by a close relationship with a number of antigens of the main histocompatibility complex (MHC, HLA in humans) involved in immunoregulatory processes (HLA DR3, HLA DR4, HLA DR7, etc.). The auto-tolerance of CD4 and CD8 T cells to hepatic autoantigens is impaired as a result of exposure to various environmental factors and the inability of autoantigen-specific natural regulatory T cells and induced regulatory T cells prevent the process of autoreactivity. At the same time, in the absence of effective inhibition of regulatory B cells, autoreactive B cells produce autoantibodies. Peptide autoantigens are represented by HLA class II and class I alleles, autoreactive T-cell receptors on CD4 T-helper cells and CD8 cytotoxic T-lymphocytes. The binding of various autoantigens to B-cell receptors initiates the secretion of specific autoantibodies [4].

Among the exogenous etiological factors of AIH, the role of Epstein-Barr viruses, measles, hepatitis A and C, as well as some drugs (minocycline, nitrofurantoin, melatonin, etc.) is also discussed in the medical literature. The possibility of AIH due to a primary conditioned violation of the immune response when the appearance of autoreactive cells occurs without exposure is not excluded trigger factors. This interaction induces T-cell immune responses against hepatocyte antigens, which leads to the development of progressive inflammatory and fibrotic changes in the liver, which is confirmed by the studies of A. J. Czaja et al (2020) [5].

The following types of AIH are distinguished: Type I AIH (AIH-1), which is the predominant type of this pathology in both adults and children, is characterized by a positive reaction to antinuclear antibodies (ANA) and/or antibodies against smooth muscles (anti-SMA), which can be detected in 80% and 63% of patients, respectively, AIH Type II (5-10% of cases), occurs mainly in children and is characterized by the presence of microsomal antibodies to type 1 liver/kidneys (anti-LKM1) and/or antibodies to type 1 liver cytosol (anti LC-1) [6].

Autoimmune hepatitis type II can clinically manifest as signs of acute or chronic hepatitis, in the absence of specific symptoms. Complaints are usually associated with increasing hepatic cell insufficiency. The main symptoms are: fatigue, malaise, fever, jaundice, nausea, hepatomegaly, itching, telangiectasia, ascites, splenomegaly, abdominal pain. Standard induction therapy for type II AIH includes a combination of high doses of glucocorticosteroids (GCS), sometimes in combination with azathioprine. Currently, research is underway on other drugs (infliximab, budesonide, rituximab and others), however, standard induction therapy is the gold standard for the treatment of type II AIH [6,9,10]. The general goal of type II AIH treatment is to induce and maintain complete suppression of inflammatory activity and prevent the progression of the disease to cirrhosis of the liver [7].

The Clinical Case

A girl M. 2012, from the 3rd pregnancy, the 1st delivery, with a body weight – 3700 g, a body length – 57 cm. The patient was breastfed for up to 6 months. Preventive vaccinations were carried out according to the National Vaccination Calendar. It is known from the medical history that at the age of 7 years old, the girl was diagnosed diabetes mellitus type I (DM1) at the preclinical stage. During a routine examination after an acute respiratory viral infection, the girl was diagnosed with glycaemia of 8.0 mmol/l in the absence of complaints and clinical symptoms. During an in-depth examination (04/24/2019), antibodies to GAD and IA2, IgG >450 IU/ml (N - <4 IU/ml), antibodies to insulin, IgG – 31.67 IU/ml (N - <10 IU/ml), antibodies to pancreatic cells, IgG titer 1:4 (positive result). Clinical symptoms of diabetes appeared 4 months later – in September 2019. The examination revealed hyperglycemia – 18.5 mmol/l, the level of glycated hemoglobin – 8.0%, glucosuria – 1.3%. Ultrasound examination of the abdominal organs revealed no pathology. In 2021 (age of 9 years old) due to the difficulty of selecting adequate therapy and limiting the administration of insulin using syringe pens, the patient was transferred to pump insulin therapy.

In October 2021, the child had multiple vomiting after eating, and the district pediatrician prescribed sorbents with insignificant positive dynamics. In the future, the girl's condition worsened, her parents noted jaundice of the sclera and skin, darkening of urine. Considering the severity of the condition on 16.10.2021, the girl was hospitalized in the infectious diseases department of the Regional Children's Clinical Hospital named after N. V. Dmitrieva in Ryazan [8]. Biochemical blood tests revealed pathological changes: hyperbilirubinemia (due to indirect fraction), hypertransaminasemia, and an increase in gamma-glutamyltransferasemia. Increased immunological activity of anti-LKM1 was detected. According to the results of a computer tomography (CT) of the abdominal cavity (17.10.2021), the following signs of liver cirrhosis, hepatomegaly, splenomegaly were revealed. Based on the examination, the patient was diagnosed with type II AIH. Infusion therapy (reambirin, 10% glucose solution) and hepatoprotective therapy (ursodeoxycholic acid (UDCA)) were prescribed in the hospital. Against the background of the treatment received, the patient's condition stabilized, and planned hospitalization was recommended at the Federal Research Center for Nutrition, Biotechnology and Food Safety in Moscow. The results of laboratory parameters before and after treatment are presented in Tables 1, 2.

Table 1: The Results of Biochemical Blood Analysis of Patient M. in Dynamics

Parameter	16.10.21	12.11.21	11.12.21	30.12.21	25.05.24	Reference values
Glucose (mmol/l)	13	15	7.5	8.1	7.43	3.9-5.8
AST (IU/l)	409	185	162	91	50	4-40
ALT (IU/l)	557	133	87	95	41	4-40
GGT (IU/l)	153	55	113	55	20	10-60
LDG (IU/l)	450	477	387	-	-	225-400
Total billirubin (mkmol/l)	200	81	18	17	10	8-20
Direct billirubin (mkmol/l)	113	61	12	7	3.5	0-5
Glycated hemoglobin (%)	8.0	7.7	7.9	8.0	9.0	4.5-.0
IgG (g/l)	-	9.8	9.3	8.6	8.1	6.8-16.5

Table 2: The Results of Changes in the Anti-lkm1 Indicators of Patient m. in Dynamics

Parameter	16.10.21	11.12.21	30.12.21	25.05.24	Reference values
anti-LKM1 (IU/ml)	305	305	30	39	≤20

A month later (11.12.2021), the patient was hospitalized as planned at the Federal Research Center for Nutrition, Biotechnology and Food Safety (Moscow), to determine further tactics for the management and treatment of the patient. At the time of hospitalization, the child's condition was of moderate severity, due to persistent cytolysis and cholestasis syndromes, and the development of coagulopathy (prothrombin index 40%). According to the results of ultrasound of the abdominal cavity (12.12.2021), there were signs of cirrhosis of the liver, hepatomegaly, splenomegaly, ascites. Considering the patient's condition, the results of laboratory tests, as well as the minimal effectiveness of previously received treatment, it was decided to prescribe systemic GCS (prednisone at a dose of 30 mg / day).

Against the background of complex therapy (antibacterial, antioxidant, immunosuppressive, hepatoprotective), restoration of protein-synthetic liver function, normalization of homeostasis was noted, which allowed gradually reducing the dosage of prednisolone to 11.25 mg/day. However, despite the therapy, the patient maintained a high level of glycated hemoglobin and unstable glycemic indices. The girl was discharged in satisfactory condition, under the outpatient supervision of a pediatrician, gastroenterologist, endocrinologist, at her place of residence. The results of the studied parameters before and after treatment are shown in Table 1, 2.

Two years later (05.25.2024), during a routine examination, the girl's condition showed a positive trend in significant biochemical parameters. However, the level of glycated hemoglobin and blood glucose exceeded the threshold values. Minimal immunological activity is also maintained. These results are presented in Table 1, 2. During a routine examination by an endocrinologist (07.26.2024.) the somatic status indicates the presence of symptoms of the drug-induced Itsenko-Cushing syndrome (overweight Z-Score 1.24, black acanthosis of the neck) [9]. According to the results of ultrasound of the abdominal cavity, there is a decrease in liver fibrosis from F2 to F1 (according to the Metavir scale). Based on the obtained research data, the dosage of prednisolone was reduced to 5 mg/day. The patient is regularly monitored at the Federal Research Center for Nutrition, Biotechnology and Food Safety (Moscow) to assess the course of the disease and correct further treatment. At the moment, the patient's condition is satisfactory, she does not complain, receives insulin therapy in a pump mode (40-55 IU/day), prednisone 5 mg/day, hepatoprotectors.

Discussion

AIH is a disease with unknown etiology characterized by elevated levels of aminotransferases and Ig G, as well as the presence of autoantibodies and a histological picture of interface hepatitis [10]. In the clinical case presented by us, there was an acute manifestation of type II AIH in a patient born in 2012. At the same time, the choice of treatment tactics was complicated by the presence of diabetes mellitus type I. Since the main drug for the treatment of AIH is GCS, the pharmacological effect of which complicates the control of glycaemia in type I diabetes. Which required continuous monitoring of blood glucose levels. Depending on the severity of the disease, there are several main lines of type II AIH therapy. Standard treatment of AIH in children includes GCS with a higher initial dose, compared with adult patients, in order to quickly suppress the autoimmune response in parallel with a decrease in the level of aminotransferases [11].

Z.J. Yu et al (2019) recommended as the starting therapy of AIH are hormonal and immunosuppressive therapy. Complete stabilization of the level of aminotransferases and serum IgG is considered a favorable response to treatment. Partial normalization of biochemical parameters or intolerance to starting therapy is an indication for the appointment of a second line of immunosuppression (mycophenolate mofetil). In the clinical case presented by us, against the background of taking prednisone 30 mg/day. There was a decrease in the level of aminotransferases by half. Currently, clinical and hematological remission is observed, the dose of prednisolone is 5 mg/day.

The combination of type II AIH in children is a rather rare condition and is not often found in the medical literature. T.I. Legonkova et al. (2023) presented a clinical case of AIH, a patient with an acute onset of the disease with a high level of amino-

transferases, the starting dose of methylprednisolone was 4 mg/day, azathioprine was included in immunosuppressive therapy at a dosage of 25 mg/day. Against the background of the treatment, there was a significant improvement in the patient's well-being and normalization of biochemical blood parameters [12].

A clinical case of type II AIH development in a girl 11 months after a new coronavirus infection was also described in the literature. However, the manifestation of the disease occurred without pronounced cholestasis syndrome, the parameters of bilirubin were within the normal range, but the level of aminotransferases significantly exceeded the reference values (AST/ALT=1794/1777 IU/l). As in the previous case, against the background of immunosuppressive therapy (prednisone and azathioprine) The patient achieved clinical and hematological remission [13].

In our clinical case, the appointment of immunosuppressive therapy was not necessary, since against the background of therapy with systemic GCS, it was possible to stop the progression of liver cirrhosis. The clinical case of AIH development in a girl suffering from diabetes type I presented by us demonstrates the peculiarities of the course of not only AIH, but also the underlying disease, the therapy of which is significantly complicated. Due to the fact that the drug-induced Itsenko-Cushing syndrome develops against the background of basic AIH therapy. One of the main links in the pathogenesis of the latter is an increase in blood glucose levels due to the activation of gluconeogenesis and glycogenogenolysis. The presence of two or more autoimmune pathologies, type II AIH and diabetes of type I, provides for autoimmune polyglandular syndrome (APS), which is confirmed by studies by I.V. Sichinava et al. (2022), according to which AIH was one of the leading manifestations in the manifestation of APS [14].

However, studies conducted by M.A. Sperling et al (2024) claim that the diagnosis of APS is made in the presence of 2 out of 3 classic signs (autoimmune thyroiditis, Adisson's disease, cutaneous mucosal candidiasis). It is possible that this child has an unspecified variant of APS. Confirmation or refutation of the presence of APS in the presented clinical case requires further research and observation.

In presented clinical case, GCS was a fairly effective method of therapy, but this is not always noted. In some cases, drug treatment is ineffective and liver transplantation remains the only treatment option for the patient. But, however, as the data of medical studies conducted with type II AIH show, transplantation does not always lead to a favorable result, since the risk of transplant rejection remains high enough [15].

In studies conducted by E. Couchonnal et al. (2020), during which 30 children (18 girls and 12 boys) suffering from AIH were observed, the main indications for liver transplantation were acute or end-stage liver failure. At the same time, transplant rejection occurred in 19 patients, re-transplantation was required in 6 patients, and recurrence of the underlying disease was observed in 6 patients. The average survival rate after transplantation was 25-30 years.

Conclusion

Currently, the combination of type I diabetes and type II AIH is a rare condition that requires combination therapy. The prognosis for this condition is relatively favorable, provided the immunological status is suppressed. The demonstrated clinical case is a vivid example of the fact that timely diagnosis and adequately prescribed therapy can stop the progression of liver cirrhosis and achieve remission.

Informed Consent

The authors state that the patient has given his informed consent to the publication of this clinical observation.

Conflict of Interest

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Information About the Contribution of the Authors to the Writing of the Article

Research concept – Belykh N.A., writing the text - Deeva Y.V., Kondyurov E.E.; data collection – Deeva Y.V., Kondyurov E.E.; literature review – Kondyurov E.E.; writing the text - all authors; editing – Belykh N.A., Deeva Yu.V., Pisnyur I.V.; approval of the final version of the article, responsibility for the integrity of all parts of the article - all authors.

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