Autoimmune liver disease and therapy in childhood

Avtoimunske bolezni jeter pri otrocih in zdravljenje

Matjaž Homan

University Children's Hospital, Bohoričeva 20, 1000 Ljubljana, Slovenia

Korespondenca/ Correspondence:
Matjaž Homan MD PhD, University Children's Hospital, Bohoričeva 20, 1000 Ljubljana
Phone: +386 1 5229276
matjaz.homan@guest.arnes.si

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Abstract

Autoimmune hepatitis is a chronic immune-mediated disease of the liver. In childhood, autoimmune liver disorders include autoimmune hepatitis type I and II, autoimmune sclerosing cholangitis, Coombs-positive giant cell hepatitis, and *de novo* autoimmune hepatitis after liver transplantation. Autoimmune liver disease has a more aggressive course in children, especially autoimmune hepatitis type II. Standard therapy is a combination of corticosteroids and azathioprine. Around 80 % of children with autoimmune liver disease show a rapid response to combination therapy. The non-responders are treated with more potent drugs, otherwise autoimmune disease progresses to cirrhosis of the liver and the child needs liver transplantation as rescue therapy.

Izvleček

Avtoimunski hepatitis je kronična avtoimunska bolezen jeter. Pri otrocih delimo avtoimunske bolezni jeter na avtoimunski hepatitis tipa I in II, avtoimunski skleozantni holangitis, Coombs--pozitivni gigantocelularni hepatitis in *de novo* avtoimunski hepatitis, ki se razvije po presaditvi jeter. Avtoimunske bolezni jeter napredujejo pri otrocih hitreje kot pri odraslih, še posebno, če gre za avtoimunski hepatitis tipa II. Običajno zdravimo bolnike z avtoimunskimi boleznimi jeter s kortikosteroidi in azatioprimom, s čimer dosežemo remisijo pri 80 % bolnikov. Če avtoimunskega procesa v jetrih ne zaustavimo s klasičnim zdravljenjem, uvedemo močnejša imunosupresivna zdravila. Če se kljub temu razvije jetrna ciroza, je pri otroku potrebna presaditev jeter.

Introduction

Autoimmune liver diseases (ALD) are characterized serologically by auto antibodies against liver- and/or organ-specific antigens, and histologically by dense mononuclear and plasma cell infiltrates in the portal tracts.[1] Although these diseases are considered to be of autoimmune origin, the etiology and possible environmental triggers remain unrecognised. The prevalence of ALD in pediatric population is unknown, but seems to be increasing in the developed world. The four main categories of pediatric autoimmune liver diseases are autoimmune hepatitis (AIH), autoimmune sclerosing cholangitis (AISC), Coombs-positive giant cell hepatitis, and *de novo* autoimmune hepatitis.

Autoimmune hepatitis

Epidemiology

The worldwide prevalence of AIH in adults and also in pediatric population is unknown. The autoimmune disease is mostly described in Europe, North America and Japan and accounts for 20 % of diagnosed patients with chronic hepatitis.[2] In studies from Europe, the roughly estimated incidence is 0.9 to 2 per 100,000 population per year.[3] It is at least threefold more common in girls than in boys. The search for predisposing genetic factors has focused on the DR3 and DR4 histocompatibility genes. In patients from Europe AIH is associated with the HLA A1-B8-DR3 haplotype, especially with DR3. In Japan it is primarily as-

sociated with the DR4 haplotype. It looks as if HLA DR3 predisposes to an earlier onset of AIH and to more aggressive autoimmune disease.[4]

Classification and serological assessment

According to the antibody profile, we differentiate between AIH type I and AIH type II. Classic (type I) AIH is positive for anti-nuclear (ANA) and/or anti-smooth muscle (ASMA) antibodies. Anti-liver kidney microsomal antibody type I (anti-LKM_1) is detected in AIH type II.

Other antibodies that can be useful in defining AI hepatitis are anti-SLA, anti-LKM_3, atypical p-ANCA and anti-LC_1. In children, even low titers 1 : 20 for ANA and ASMA, and 1 : 10 for anti-LKM_1 are clinically relevant. Furthermore, anti-LKM_1 in high titers strongly suggests the diagnosis of AIH type II, even if liver histology is not typical for ALD. Titers are useful for monitoring the response to specific therapy only in pediatric patients.[5]

In a minority of children with ALD, all types of antibodies are negative and response to immunosuppressive drugs ultimately confirms AI hepatitis. This group of patients may be more easily diagnosed in the future when other characteristic antibodies for autoimmune disease will be described.

Clinical, laboratory and histological assessment

ALD has more aggressive course in children than in adults. In more than 40 % of cases, the clinical picture is similar to acute viral hepatitis, and especially young children with AIH type II are prone to develop acute liver failure.[6] The onset is insidious in 40 % of children with ALD. Fatigue, jaundice and weight loss progress slowly, and it takes several months before a child comes to the hospital. We suspect ALD in a minority of patients who present with complications of long lasting liver disease such as hematemesis, bleeding diathesis and splenomegaly.

The clinical picture is heterogeneous and in absence of a single diagnostic test, diagnosis is made according to a set of biochemical and histological criteria developed 20 years ago but revised in years 1999 and 2008.[7-9] The utility of simplified criteria based on the positive auto antibodies, IgG and histology were also evaluated in children with ALD.[10] The conclusions were that simplified scoring system in children is quite specific, but it cannot differentiate between AIH and AISC. The key diagnostic feature for AIH is the high titer of characteristic antibodies. The positivity of titers alone is not sufficient for diagnosis of AIH because they can be present in low titers in other liver diseases such as Wilson disease, non-alcoholic steatohepatitis, and hepatitis B and C as well.[11-13]

Hyper IgG is quite typical for ALD in childhood, but there are some case reports of children with normal IgG levels and diagnosis of AI hepatitis.[6] The level of IgG is also a good marker for the activity of autoimmune disease. Low C_4 is a predisposing factor for ALD[14]. IgA deficiency is more typical for AIH type II than AIH type I.[15]

To confirm the diagnosis and to influence a treatment decision, it is necessary to perform liver biopsy at presentation of the AI disease. In cases of acute liver failure, even if liver biopsy was not performed, the specific therapy must be started immediately in order to stop the autoimmune process. No histological finding is specific for AIH, but plasma cell infiltration and interface hepatitis are quite characteristic for ALD. In the beginning, fibrosis of the liver is present and if the disease progresses, bridging fibrosis and finally cirrhosis develop. The findings of steatosis or iron overload may suggest an alternative diagnosis.

Concurrent immune diseases are possible with AIH, such as autoimmune thyroiditis, type I diabetes mellitus, vitiligo, and especially ulcerative colitis.

Autoimmune sclerosing cholangitis

It was shown that approximately 50 % of children with ALD have alterations of the bile ducts, though less advanced than described in adult primary sclerosing cholangitis.[16] AISC affects boys and girls equal-

ly.[16] In general, children with AISC have high IgG, and inflammatory bowel disease is present in almost half of patients. In contrast to AIH, all patients with AISC are seropositive. In pediatrics, AISC is often not associated with elevated alkaline phosphatase or γ-glutamyl transpeptidase in the beginning. The diagnosis of AISC relies on biliary changes showed in cholangiographic studies. Cholangiographic studies should be performed in all children with AIH to exclude AISC.[5]

Coombs-positive giant cell hepatitis

Coombs-positive giant cell hepatitis is a very rare disease with early age onset and severe clinical course. It develops mostly between 6–24 months of age and the characteristics are profound anemia, cholestatic jaundice and typical histological changes. Liver biopsy reveals extensive giant cell transformation with fibrosis. The antibodies typical of AIH are not present.[17] The disease may be related to syncytial giant cell hepatitis, although viral studies are generally negative.[18] Usually the disease is treated with corticosteroids and azathioprine. The Coombs-positive giant cell hepatitis is frequently refractory to immunosuppresive therapy and liver transplantation must be performed. Morover, the disease may recur after liver transplantation.

De-novo autoimmune hepatitis

Fifteen years ago it was discovered that AIH can develop in transplanted liver in children who had not been transplanted for.[19] Characteristics are completely the same as in classical ALD, with elevated liver enzymes, typical serology and interface hepatitis. Analysis of the HLA phenotypes showed that in the majority of cases the recipients received livers with HLA susceptibility markers for.[19]

Treatment

In contrast to adults, all children with ALD should be treated since the autoimmune disease is more aggressive in pediatric population. The only exceptions are children with advanced cirrhosis with no evidence of inflammation, who probably do not benefit from therapy. Almost 50 % of children have cirrhosis at the time of diagnosis, most probably due to delays in defining ALD.[20] Standard treatment of ALD is with corticosteroids alone or in combination with azathioprine.[21] The response to classical therapy is excellent in children with ALD. The recommendation of American Association for the Study of Liver Diseases is to start with prednisone (1–2 mg/kg daily; maximum dose 60 mg daily) in combination with azathioprine (1–2 mg/kg daily) or 6-mercaptopurine (1.5 mg/kg daily).[20] The use of ursodeoxycholic acid is recommended in AISC, but more studies should be done to define its role in treating children with AIH. Corticosteroids are very effective, but not very popular in children due to many and severe adverse effects. Therefore the prednisone dose should be lowered as soon as possible, but no earlier than after two weeks. Over a period of 4–8 weeks the prednisone is gradually decreased to the average minimum dosage of 5 mg/day or 0.1–0.2 mg/kg/day. Usually, azathioprine or 6-mercaptopurine is added when AST decreases to 2–3 times the normal range. Remission occurs when there is improvement in liver enzymes to less than twice the normal levels, normalization of IgG and when the histology shows only minimal inflammation with no interface hepatitis. It may take either a few weeks or a few years to fulfill remission criteria (median time 0.5 years in AIH type 1 and 0.8 years in AIH type 2).[22] The risk factors for treatment failure are diagnosis at young age, a high serum bilirubin level at diagnosis, no improvement after 2 weeks of maximal corticosteroid therapy, long duration of the disease, presence of HLA-B8 or HLA-D3 phenotype, and cirrhosis of the liver at initial biopsy.[1,23] Therapy with prednisone alone is advocated in children with cytopenia, malignancy, known total deficiency of methyltransferase and in pregnant adolescents, because azathioprine has possible myelosuppresive, oncogenic and teratogenic actions.[24] After a child has been in re-

mission for at least 2–3 years, a control liver biopsy is performed and if there is none or only minor histological evidence of inflammation, the therapy can be withdrawn. The percentage of sustained remission after withdrawal of the drug depends on the time of continuous treatment.[25] In addition, the weaning must be slow (azathioprine by 25 mg every month, prednisolone 2.5 mg every 3 months). Regular and frequent monitoring of liver tests should be performed after cessation of the drug. If the adolescent is near or during puberty, it is not wise to withdraw therapy, because relapse is more common. The good candidates for drug withdrawal are patients before or after puberty with AI hepatitis type 1 and a long period of remission.

Patients, who failed to achieve remission with standard therapy and progress toward cirrhosis finally require liver transplantation. Conditions, such as Wilson disease and chronic hepatitis C, must be re-considered at the time of therapy failure. In adolescents, non-adherence to treatment is also possible as the cause of therapy failure. In non-responders to classic therapy with re--confirmed ALD, a more potent immunosuppressant should be used.[26] While there is an international consensus on the first-line therapy for ALD, there is no agreement regarding the therapy of patients with treatment failure or suboptimal response to classic therapy for ALD. Calcineurin inhibitors Ciclosporin and Tacrolimus as well as purine antagonists Mycophenolate mofetil can be used as salvage therapy.[27] In addition, Cyclophosphamide[28], methotrexate[29], rapamycin[30] and rituximab[31] have been tried as possible therapies with limited success in ALD in small studies.

Corticosteroid-related side effects are the most common cause for premature drug withdrawal in ALD.[5] Cosmetic changes, striae, weight gain, acne and alopecia occur in 80 % of patients after 2 years of corticosteroid treatment. Adolescents are very sensitive, especially to the cosmetic side effects. Severe adverse effects such as vertebral compression due to osteoporosis, diabetes, psychosis, pancreatitis and stunted growth are also possible in pediatric population after long lasting corticosteroid therapy. Due to the long list of severe corticosteroid adverse effects, new drugs are tested to replace standard drugs in ALD therapy protocols. Budesonide (BUD) is a second generation corticosteroid with a 15-times higher affinity for the glucocorticoid receptor than prednisolone. It has very few side effects because 90 % of the drug metabolizes with its first pass through the liver. In a small study, Wiegand et al. proved that 'topical' steroid therapy is effective in previously untreated patients with ALD.[32] Zandieh et al. reviewed experiences about using BUD in AIH patients in Canada.[33] A total of nine females with AIH were identified. In 7 out of 9 patients BUD successfully normalized liver enzymes. In a German study, eighteen patients with AIH were treated with BUD 9 mg daily for at least 6 months.[34] The conclusions were that BUD was able to induce remission in therapy-naive patients as well as in patients where standard therapy failed or the patients became intolerant to these drugs. In addition, the therapy is efficient also in overlap syndrome cases. Side effects and treatment failure were observed in patients with liver cirrhosis. Because of poor drug metabolism in the liver, BUD is probably contraindicated in patients with cirrhosis. In a large multicentre European study published in 2010, patients with non-cirrhotic ALD treated with BUD and azathioprine, responded better than patients treated with standard therapy prednisolone and azathioprine.[35] More than 200 treatment-naive patients with AIH were included. After 12 months remission occurred in 50 % of BUD patients versus 41 % of prednisone group of included patients. Furthermore, the frequency of adverse effects was twice lower in BUD group of patients. There are some limitations of the study. The remission rate in prednisone group was very low. In addittion, the study protocols for both groups of patients were different in favor of BUD group. To induce remission in non--cirrhotic ALD patients, BUD may become an alternative therapy to prednisolone in the future.

Conclusion

ALD are progressive inflammatory disorders of the liver, affecting mainly girls. In children, even low titers of autoantibodies are diagnostic. Most children with ALD should undergo cholangiographic studies to exclude AISC. In addition to liver enzymes, titers of autoantibodies and IgG levels are useful biomarkers of disease activity as well. All children with ALD must be treated as soon as possible because the course of disease in pediatric patients is very aggressive. Standard and most used therapy in children with ALD is still based on corticosteroids and azathioprine.

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