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ORIGINAL ARTICLE

Autoimmune hepatitis type II in child

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Abstract

Autoimmune hepatitis (IHD) consists of severe liver disease, occurring in both adults and children, being particularly aggressive in childhood. This condition can be divided into two forms: autoimmune hepatitis type I and autoimmune hepatitis type II, and what differentiates the two forms is the presence of autoantibodies. With regard to age, some studies have found that children with type 2 AIH were significantly younger than those with type 1 AI, both in Brazilian, British, and Egyptian populations. The pathogenesis is still not very clear, however it is known that environmental factors not yet identified, viruses and, occasionally, drugs can trigger the disease in genetically susceptible individuals. The clinical spectrum of the disease is broad, ranging from asymptomatic individuals with impaired hepatic function to those with fulminant hepatic insufficiency. The diagnosis is based on a combination of clinical, biochemical and histological parameters and the exclusion of other liver diseases. It is a relatively rare but devastating disease that progresses rapidly unless immunosuppressive treatment is started promptly. Standard therapy consists of a combination of corticosteroids and azathioprine, which is effective in 80% of patients. Autoimmune hepatitis remains an important cause of liver disease in the pediatric age group. Thus, physicians should consider this fact in the differential diagnosis of liver diseases, especially in asymptomatic children with elevated levels of hepatic transaminases, those with insidious liver disease, and those with hepatomegaly or hepatosplenomegaly, when other conditions are excluded.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a severe liver disease particularly aggressive during childhood that affects individuals of all ages[1]. The condition is divided into types 1 and 2, which are distinguished based on the presence of certain autoantibodies[2].

Studies carried out in Brazil, Britain, and Egypt found that children with type 2 AIH were significantly younger than children with type 1 AIH.[1,3]

The pathogenesis of AIH is still unclear, but environmental factors yet unidentified, viruses, and occasionally drugs may trigger the disease in genetically susceptible individuals[4,5]. The spectrum of clinical manifestations is broad, ranging from asymptomatic individuals with impaired liver function to patients with fulminant hepatic failure. Diagnosis is based on a combination of clinical, biochemical, and histological parameters and the exclusion of other liver diseases. AIH is a relatively rare but devastating disease that progresses rapidly unless immunosuppressive therapy is promptly initiated. Standard therapy consists of a combination of corticosteroids and azathioprine, which is effective for 80% of the patients[1,2,4-6].

AIH remains an important cause of liver disease in childhood, and cannot be neglected by physicians in the list of liver diseases considered for purposes of differential diagnosis, especially when providing care to asymptomatic children with elevated hepatic transaminases, patients with silent liver disease, and individuals with hepatomegaly or hepatosplenomegaly when other conditions have been ruled out[7].

This report describes the case of a child diagnosed with early-stage autoimmune hepatitis during a routine visit.

CASE REPORT

A Caucasian female child aged 25 months with hepatosplenomegaly for a month arrived at our center presenting apathy, hyporexia, a distended abdomen not associated with fever, weight loss, jaundice, choluria, and acholic feces. The child was previously healthy.

Her neonatal life was uneventful and she was within the normal growth range expected for her age. No familial disease was reported.

Physical examination showed she was in good general condition and free of cardiovascular and respiratory disorders. Her liver was 3 cm below the right costal margin and her spleen was 1 cm below the left costal margin.

Abdominal ultrasound examination showed mild unspecific liver tissue heterogeneity indicative of liver disease, in addition to mild homogeneous splenomegaly.

The patient had negative serology for hepatitis A, B, C; Epstein-Barr virus; HIV; toxoplasmosis; dengue; and cytomegalovirus. Her ceruloplasmin, alpha-1-antitrypsin, and serum copper levels were normal.

Her complete blood count revealed she had mild thrombocytopenia, which worsened after one month. Her antinuclear antibody and anti-smooth muscle antibody tests came back negative. However, she had a high titer of anti-LKM antibodies. Therefore, the patient was suspected for type 2 AIH.

Additional workup showed her bilirubin levels were unaltered. Hepatic transaminases were elevated, with the first test showing GOT: 232 and GPT: 895; tests run a month later read GOT: 854 and GPT: 1426. The levels of hepatic transaminases decreased after the start of treatment and have since been close to reference values. Her total protein levels were unaltered at first and decreased later, while albumin levels were normal. No alteration was observed in coagulation tests. The patient did not undergo a liver biopsy on account of technical limitations present in our center. The patient was diagnosed with type 2 AIH and was started on methylprednisolone 2mg/Kg/day and azathioprine 1-2 mg/Kg/day.

DISCUSSION

AIH is a disease that affects the liver parenchyma in acute or chronic presentations. For purposes of practicality, the disease was divided into two subtypes with distinct disorders based on antibody profiles[2]. Type 2 AIH is less common and has been associated with the presence of anti-LKM or anti-LC1 antibodies[2,5] in adults and children, with anti-LKM1 being the more prevalent[8]. AIH manifests as an acute, more aggressive condition in children[5]. Three quarters of the children with AIH are females[5].

The etiology of AIH has been linked to a number of viruses, such as the Hepatitis A, C, and E viruses, and the measles, Epstein-Barr, and Herpes simplex viruses. It has been reported that in type 2 AIH, anti-LKM-1 antibodies target a number of epitopes on hepatic cytochromes, specifically CYP2D6[2], which presents a structure homologous to the hepatitis C virus, cytomegalovirus, and herpes simplex virus 1[9]. These findings indicate that these viruses may trigger liver autoimmunity.

In addition to viruses, drugs have been linked to the onset of autoimmune hepatitis, such as minocycline, tienilic acid, nitrofurantoin, melatonin, diclofenac, propylthiouracil, and statins[2]. Most of the drugs associated to drug-induced AIH are not included in prescriptions to children, with minocycline ranking as the medication most frequently associated to the onset of AIH[10]. Our patient did not have evident risk factors for developing type 2 AIH.

Cases of genetic predisposition to type 2 AIH have been described in the literature[5,11,12].

In recent years, studies have discussed the role of regulatory T-cells in the pathophysiology of autoimmune hepatitis. Multiple triggers have been identified, with the disease reportedly developing in genetically susceptible individuals[2]. Although the mechanisms leading to the breakdown of immune tolerance in individuals with autoimmune hepatitis have not been entirely described, the involvement of immune

regulation is likely to play an important role in autoimmunity.

In healthy individuals there is a balance between regulatory T cells promoting immune tolerance to liver autoantigens and effector cells triggering immune responses against autoantigens[2]. If regulatory T cells are impaired and effector cells are thus not adequately regulated or suppressed, immune tolerance to liver autoantigens is lost and autoimmunity sets in and perpetuates autoimmune damage[2].

Therefore, one may infer that although susceptibility to autoimmune disease is multifactorial, genetic and immune factors play a crucial role in autoimmunity[13].

The clinical manifestations of autoimmune hepatitis vary. Most pediatric patients have unspecific symptoms such as anorexia, malaise, and abdominal pain, at times progressing to jaundice, choluria, and acholic feces[5,14].

Others may present with progressive fatigue, recurring jaundice, headaches, anorexia, amenorrhea, and weight loss, in cases where the disease develops more silently. Other patients may be diagnosed after suffering from complications arising from portal hypertension such as splenomegaly, hematemesis, bleeding diathesis, chronic diarrhea, and weight loss[5]. However, most of the patients show signs of chronic liver disease during physical examination, including skin stigmata, hardening of the liver, and splenomegaly. Reports indicate that patients positive for anti-LKM may suffer from acute liver failure and ensuing complications such as hepatic encephalopathy within two to eight weeks from the onset of the disease[5].

Ultrasound examination may at times reveal a nodular heterogeneous liver parenchyma[5].

The diagnosis of autoimmune hepatitis is based on the criteria developed by the International Autoimmune Hepatitis Group (IAIHG)[2,5,15,16]. The diagnostic criteria for autoimmune hepatitis were created in 1992 and updated in 1999[16]. Our patient had elevated transaminases, was positive for anti-LKM antibodies, negative for infection by hepatitis A, B, or C, and entered remission after receiving treatment for the condition.

The diagnostic criteria were originally developed for purposes of research and were adapted for use in clinical practice. The weights assigned to clinical, biochemical, and histology variables, along with the levels of response to treatment, define patients as having definite, probable, or no autoimmune hepatitis based on the scores below Table 1[2,5]:

A simplified set of criteria based on detectable autoantibodies, immunoglobulin G levels, histology, and exclusion of viral hepatitis was launched in 2008. The simplified criteria have been independently validated and were considered more adequate for use in clinical practice. The sensitivity and specificity of the criteria are above 80% and 95%, respectively[4,15-17].

Transaminase levels twice the normal and liver biopsy findings suggestive of disease should prompt the start of treatment to prevent AIH progression[2,5]. Nonetheless, patients should always be treated when presenting acute increases in GOT or GPT to levels ten times greater than the upper reference limit, evidence of multilobular or bridging necrosis, or severe hepatic or extrahepatic symptoms[2]. Our patient had transaminase levels ten times greater than the upper reference limit, a finding that prompted the start of therapy.

The conventional treatment of pediatric autoimmune hepatitis consists of prednisolone or prednisone 2 mg/kg/day, with a maximum of 60 mg/kg/day. The dose of medication is tapered within the course of four to eight weeks as transaminases decline[5]. Azathioprine is often prescribed to decrease the dosage and use of corticosteroids, mainly if transaminase levels fail to fall with the isolated use of corticosteroids or if severe side effects arise from the use of corticosteroids[5].

Corticosteroids, with or without azathioprine, have been associated with remission in about 85% of the cases, and thus became the standard therapy for AIH[2]. The goal of treatment is to eliminate or decrease liver inflammation, thus improving symptoms and increasing survival[2,5].

Although the association between remission from AIH and immunosuppressant therapy has been established, it is unclear whether immunosuppressants can be entirely suspended. It has been shown that immunosuppressants can only be stopped after sustained biochemical and histological remission for a minimum of two years. Only then can patients be gradually weaned[2]. It is recommended that patients considered for cessation of therapy undergo liver biopsy[18].

CONCLUSION

Autoimmune hepatitis is a disease that affects children and adults, with more aggressive manifestations observed in younger patients. However, if diagnosed and treated in its early stages, AIH may offer patients a more favorable prognosis with few individuals requiring a liver transplant.

Subjects showing signs of liver disease in which more common conditions have been ruled out should be suspected for AIH and provided treatment promptly.

Further studies are required to clarify the pathogenesis of the disease so that less aggressive - and possibly more promising - therapies are instituted for patients with AIH.

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Table 1. Modified diagnostic scoring for the diagnosis of autoimmune hepatitis.

	Score
Female sex	+2
Relação fosfatase alcalina / aspartato aminotransferase (ou alanina aminotransferase)	
< 1,5	+2
1,5 - 3,0	0
> 3,0	-2
Serum concentrations of globulins or IgG above normal	
>2,0	+3
1,5 - 2,0	+2
1,0 - 1,5	+1
< 1,0	0
Titers of antinuclear antibodies anti-smooth-muscle antigen, or anti-liver-kidney microsomal antibody type 1	
> 1:80	+3
1:80	+2
1:40	+1
< 1:40	0
Positive for antimitochondrial antibody	-4
Hepatitis viral markers	
Positive	+3
Negative	-3
Drug history	
Positive	-4
Negative	+1
Average alcohol intake	
< 25 g/dia	+2
>60 g/dia	-2
Liver histology	
Interface hepatitis	+3
Predominantly lymphoplasmacytic infiltrate	+2
Rosetting of liver cells	+1
Biliary changes	-3
Atypical features	-3
None of the above	-5
Other autoimmune disease in either patient or first-degree relative	+2
Optional additional variables	
Seropositivity for other defined antibodies	+2
HLA DR3 or DR4	+1
Response to treatment	
Remission alone	+2
Remission with relapse	+3

Source: Alvarez F, Berg PA et al. J Hepatol 1999; 31: 929:938. Pretreatment scores >15: Definite AIH; 10–15: Probable AIH. Posttreatment scores: >17: Definite AIH; 12–17: Probable AIH.

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