

CASE REPORTS

AUTOIMMUNE HEPATITIS AND INFLUENZA A - A POSSIBLE ASSOCIATION

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ABSTRACT

The authors report a case of a 7-year-old white female child with respiratory infection caused by influenza A, who developed right after autoimmune hepatitis. Influenza A virus may have acted as an environmental trigger. Autoimmune hepatitis is a rare disease in children, which can progress to cirrhosis and/or liver failure if not recognized and treated early. Despite the unknown etiology, genetic factors and environmental triggers like viral infections are contributory. Diagnosis is based on laboratory markers (hypertransaminasemia, hypergammaglobulinemia, circulating autoantibodies) and characteristic histology, after exclusion of other etiologies. The investigation carried out highlights hypergammaglobulinemia, ANA (1:320) and biopsy suggestive of autoimmune hepatitis. Treatment with prednisolone and later azathioprine was started, with a favourable response. Emphasizing the importance of early initiation of treatment, allowing in most cases a good long-term prognosis.

Introduction

Autoimmunity can affect the liver through three mechanisms: autoimmune hepatitis (AIH), autoimmune sclerosing cholangitis (ASC) and de novo AIH after liver transplantation.¹ AIH is considered the prototype of liver autoimmune diseases. It is a rare chronic liver disease in children, secondary to the loss of immune tolerance towards the liver antigens, with consequent destruction of the liver parenchyma.^{2,3,4} It can appear at any age; however it is rare below 2 years old, with a higher incidence between 10 and 30 years old.^{3,5} It is predominant in females, regardless of their type.^{4,6} In AIH type 1, the female/male ratio is 4:1, but in AIH type 2 the ratio is 10:1.^{7,8} From studies carried out, in Israel and Europe, it was found that worldwide the incidence may vary between 0.7-2/100,000 inhabitants and the prevalence between 4 and 25/100,000 inhabitants.^{9,10,11,12} Although the aetiology is unknown, genetic factors contribute to autoimmune hepatitis and toxic and viral infections may act as triggers.^{6,12,13} Molecular mimicry between self-antigen epitopes and viral epitopes appears to support virus-induced AIH.¹² The literature describes the association between AIH and hepatitis A (HAV), B (HBV) or C (HCV), cytomegalovirus (CMV), the Epstein-Barr virus (EBV) and the measles virus.^{6,13} The relationship between genetics and the auto-inflammatory process is still poorly understood, apparently involving the major

histocompatibility complex (MHC), autoantigens and T cells.⁶ According to the autoantibodies present, AIH is classified as type 1 or type 2.^{3,4} In type I AIH there is the presence of anti-smooth muscle antibodies (SMA) and/or anti-nuclear antibodies (ANA); in type II AIH, anti-hepatic-renal microsome antibodies type 1 (anti-LKM 1) and/or anti-hepatic cytosol type 1 antibodies (anti-LC 1) are detected.^{3,4} This classification is currently the subject of debate, due to the recent discovery of antibodies against soluble liver antigens (anti-SLA), which are identical to antibodies against pancreas and liver (anti-LP) and therefore, called anti-SLA/ LP.¹² The clinical presentation is varied, ranging from asymptomatic cases (12–35%) and cases with fulminant acute liver failure (3–6%); there are also cases that manifest with symptoms of acute hepatitis and cases diagnosed through complications of portal hypertension (variceal bleeding, ascites, etc.), with no personal or family history of liver disease.^{1,4,5,13,14} In both AIH 1 and AIH 2, approximately 40% have a family history and 20% have a personal history of autoimmune disease present at diagnosis.^{1,12} At the time of diagnosis, 50% of children with AIH have cirrhosis, regardless of the presentation.¹² The most commonly found laboratory findings are elevation of aminotransferases (up to 50 or more times above the reference value), hypergammaglobulinemia and circulating autoantibodies.^{12,13} Liver biopsy is essential both for diagnosing and guiding the treatment of AIH and should be performed previously.¹² However, the changes found are not specific to AIH. In 1993, the international group of autoimmune hepatitis established criteria that proved to be complex in clinical practice, so in 2008, Henes et al. simplified these criteria (Table 1).¹²

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AIH is a disease that can rapidly progress to cirrhosis and/or liver failure and can require liver transplantation if not recognized and treated in a timely manner.¹² Induction treatment is performed with corticosteroids, followed by progressive weaning, with the frequent need to introduce another immunosuppressant (e.g. azathioprine).⁴ The response to treatment, with a biochemical evolution close to the reference values, is considered a diagnostic criterion together with the others mentioned.¹² Early diagnosis and treatment generally contribute to a favourable outcome.⁴ In this article, we report a case of autoimmune hepatitis diagnosed immediately after an influenza A infection in a 7-year-old patient and a literature review on clinical presentation, analytical/radiological features and outcomes.

Table 1. Simplified criteria for diagnosis of autoimmune hepatitis (Hennes et al.)¹²

| Variable | Cut-off | Points |
|----------------------------|---------------------|--------|
| ANA or SMA | =1:40 | 1 |
| ANA or SMA | =1:80 | 2 |
| Or LKM | =1:40 | 2 |
| Or SLA | Positive | 2 |
| IgG | >ULN | 1 |
| IgG | >1.10 x ULN | 2 |
| Liver histology | Compatible with AIH | 1 |
| Liver histology | Typical of AIH | 2 |
| Absence of viral hepatitis | Yes | 2 |

ANA - antinuclear antibodies; LKM - anti-hepatic-renal microsome antibodies; SLA - antibodies against soluble liver antigens; SMA - anti-smooth muscle antibodies; ULN - upper limit of normal A cut-off =6 indicates probable AIH A cut-off =7 indicates AIH

Case Report

The authors present the case of a previously healthy 7-year-old female child, seen at the Paediatric Emergency Department who had fever for 6 days,

associated with cough, headache and abdominal pain. Physical examination revealed the liver 3 cm below the right costal margin and the spleen 3 cm below the left costal margin on palpation, without jaundice. Analytical evaluation showed pancytopenia (leucocytes 1,880/uL, haemoglobin 8.3 g/dL, platelets 50,000/uL), slight elevation of C-reactive protein (1.19 mg/dL) and elevation of aminotransferases with aspartate aminotransferase (AST) of 261 U/L and alanine aminotransferase (ALT) of 226 U/L. The virus investigation in respiratory secretions by polymerase chain reaction (PCR) was positive for influenza A and negative for other viruses like adenovirus. The child was hospitalized and medicated with oseltamivir and became asymptomatic on the second day of hospitalization. In the analytical control evaluation, she showed a slight reduction in aminotransferases and improvement in pancytopenia and she was discharged on the third day. However, in the control carried out one month after discharge, there was maintenance of thrombocytopenia, anaemia (leucocytes 5,060/uL, haemoglobin 9 g/dL, platelets 126,000/uL) and an increasing pattern of aminotransferases (maximum values - AST: 600 U/L, ALT 678 U/L). (Table 2) Serology for HAV, HBV, HCV, EBV, CMV, Bartonella, Leishmania, toxoplasmosis, Mycoplasma and Chlamydia, were negative. The evaluation of autoantibodies involved in AIH was performed, with positive ANA (titre 1:320) and hypergammaglobulinemia (12 mg/dL). Ultrasound showed the liver with enlarged dimensions, bossed contours, a markedly and diffusely heterogeneous echotexture and increased portal spaces, suggesting chronic liver disease. Doppler evaluation was without changes. Liver biopsy showed lymphoplasmacytic infiltrate and interface hepatitis with bands of fibrosis suggestive of AIH, with cirrhotic evolution. Cholangiography was performed, which showed no findings suggestive of sclerosing cholangitis. The diagnosis of AIH type 1 was established and therapy with prednisolone 2 mg/Kg/day (60 mg) was started with subsequent progressive weaning, with the addition of azathioprine (0.8 mg/Kg/day), 4 weeks later, with progressive improvement in the laboratory. Twenty months after the start of therapy, the patient presented: clinical stability; recovery from

Table 2. Laboratory findings - Timeline from observation at the Paediatric Emergency Department to six months later.

| | D0 | D4 | M2 | M4 D1 PDN | M4W2 W2 PDN | M4W3 W3 PDN D1 AZA | M6 W3 PDN M2 AZA |
|----------------------|-------|-------|--------|--------------|----------------|--------------------------|------------------------|
| WBC (cells/uL) | 1880 | 4020 | 5740 | | | | |
| Hb (g/dL) | 8.3 | 8.2 | 9.8 | | 13.9 | 13.5 | 13.7 |
| Platelets (cells/uL) | 50000 | 84000 | 149000 | | 128000 | 86000 | 130000 |
| AST (U/L) | 261 | 219 | 600 | | 40 | 59 | 41 |
| ALT (U/L) | 226 | 172 | 678 | | 94 | 108 | 51 |
| CRP (mg/dl) | 1.19 | 0.35 | 0.04 | | | | |
| IgG (mg/dL) | | | 12 | | 11.8 | 9.57 | 6.64 |
| ANA (Titre) | | | 1:320 | | | | |

ALT - alanine transferase; ANA - antinuclear antibodies; AST - aspartate amino transferase; AZA - azathioprine; D - day; Hb - hemoglobin; M - month; CRP - C-reactive protein; PDN - prednisolone; W - week; WBC - white blood count.

pancytopenia; aminotransferase close to reference values; ANA (titre 1:160); gammaglobulin (6.2 mg/dL); ultrasound with portal hypertension and elastography with values suggestive of cirrhosis.

Discussion

The diagnosis of autoimmune liver diseases in paediatrics is increasingly frequent compared to the past. This fact may be related to the greater awareness and alertness of paediatricians regarding this disease.¹ AIH is an important cause of liver disease, with a particularly aggressive course.^{1,4,12} The presentation of the disease is variable, so it does not cause a great degree of suspicion.^{13,14} In the case reported, the persistence in monitoring post-discharge transaminases and the exclusion of other causes of liver disease allowed the diagnosis of AIH and the apparently timely treatment with immunosuppression, which has been maintained. The influenza A virus may have acted as an environmental trigger for the development of the disease; however, we do not know the previous values of transaminases. The most frequent histological finding at the time of diagnosis is the presence of definite or incipient cirrhosis, described in paediatric series in 59% to 100% of cases.⁵ Early initiation of treatment is the determining factor in a good long-term prognosis.⁵ In first-line treatment, remission is observed (normalization of transaminase values) in 60% to 90% of patients.¹ Treatment is with prednisolone 2 mg/kg/day (maximum 60 mg/kg/day), with the dose being reduced over 6 to 8 weeks, with monitoring of the ALT/AST7 response.¹ Azathioprine is added when the biochemical response is not adequate after 4 to 6 weeks of treatment with corticosteroids, at an initial dose of 0.5 mg/kg/day and gradual increase to 2–2.5 mg/kg/day.^{1,14} The current recommendation, according to ESPGHAN, is to maintain treatment for at least 2–3 years and consider suspending it only when transaminases and IgG are at reference values and autoantibodies are negative or at a maximum titre of 1:20, for at least 1 year.¹ Before discontinuing, a liver biopsy should be performed.¹ After discontinuing immunosuppression, patients should be monitored quarterly for 5 years.¹ The second line of treatment included mycophenolate mofetil, cyclosporine and tacrolimus.^{1,14} Liver transplantation is the treatment option for acute fulminant hepatitis or failure to respond to medical treatment, but it is important to note that the recurrence of post-transplant AIH is high (38% to 83%).¹ This case intends to raise awareness of the importance of considering AIH when there are elevated aminotransferases and the possible association with viruses, in this case influenza A.

What this case report adds

- A virus, particularly the influenza virus, may act as a trigger for autoimmune hepatitis.
- Suspicion of this disease should be increased, even in asymptomatic patients (12–35%), for early diagnosis in order to improve the prognosis.

Compliance with Ethical Standards

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Conflict of Interest None

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