Difficulties in diagnosing and managing autoimmune hepatitis in low-income countries

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Abstract

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Difficulties in diagnosing and managing autoimmune hepatitis in low-income countries

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ABSTRACT

The diagnosis of autoimmune hepatitis remains difficult in low-income countries due to the unavailability of the biopsy. autoimmune hepatitis must be retained on the basis of clinical-biological, radiological and immunological criteria. Careful trial corticosteroid therapy and diagnostic scores are essential for diagnostic autoimmune hepatitis.

Keywords: Autoimmune hepatitis, autoantibodies, immunosuppressive, Madagascar

Key clinical message

In the majority of low-resource countries, autoimmune hepatitis is retained on clinical, biological, radiological and immunological criteria. Careful trial corticosteroid therapy and diagnostic scores are essential for the diagnosis.

INTRODUCTION

Autoimmune hepatitis (AIH) is a group of diseases characterized by necro-inflammatory liver damage, the presence of specific autoantibodies, elevated γ-globulin and high sensitivity to corticosteroid therapy. Although epidemiological data are limited, the prevalence of AIH ranges from 11 to 17 per 100,000 population with a north-south gradient.[1, 2] This disease is rarely reported in sub-Saharan Africa.[1, 3] She's probably underdiagnosed. The diagnosis of AIH is based on criteria updated by the International Autoimmune Hepatitis Group (IAHG) in 1999.[2, 3] Despite the presence of these criteria, diagnosis remains difficult, especially in low-income countries.[1] Because the investigations are expensive to rule out other diseases that may resemble it. In addition, liver biopsy remains unavailable in some countries. Treatment is based on corticosteroid therapy followed by an immunomodulator.[4, 5, 6] In Madagascar, no case has yet been described on the AIH. We report two cases of autoimmune hepatitis diagnosed and followed up in a department of Gastroenterology, University Hospital Joseph Raseta Befelatanana, Antananarivo, Madagascar. We will discuss the diagnostic difficulties compared to the investigations available and the treatment compared to that currently recommended.

CASE REPORT

Case 1

A 39-year-old woman of Malagasy origin was seen in an outpatient clinic on May 24, 2018 for physical asthenia that has been evolving for 4 months. She is neither alcoholic nor smoking. The patient is allergic to peanuts. She did not report any notion of drug addiction, viral contagion, or risky sexual behavior. The patient was not taking any hepatotoxic drug. On clinical examination, she was well conscious, without asterixis. She had no signs of advanced liver disease or signs of heart failure. She did not have palpable lymphadenopathy. Laboratory studies showed hemoglobin level at 14.10 g/dL (normal range, 12-18 g/dL), leukocytes at 4.9 G/L (normal range, 4-10 G/L), platelets at 270 G/L (normal range, 150-400 G/L), alanine aminotransferase (ALT) at 661 (< 45) IU/L, aspartate aminotransferase (AST) at 597 (< 35) IU/L, γ-glutamyl-transpeptidase (γGT) at 120 (7-32) IU/L, alkaline phosphatases (ALP) at 178 (53-128) IU/L, total bilirubin at 16.9 (< 18.8) µmol/L, albuminemia at 46.83 (40.20-47.60) g/l, prothrombin level at 100% (70-100%), International Normalized Ratio (INR) at 0.949 (0.80-1.30), serum creatinine at 66 (44-97) µmol/L, C-reactive Protein (CRP) at 14.9 (0-5) mg/L, serum ferritin at 576.70 (4.63-204) ng/mL and γ-globulin at 24.84 (8-13.5) g/L. Abdominal ultrasound showed normal liver parenchyma with no focal lesions, absence of bile ducts dilation and absence of intrahepatic stones (Image 1a). Hepatitis viral markers A, B, C and E were negative. The polymerase chain reaction (PCR) were negative for cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein bar virus (EBV). The serum transferrin saturation, serum ceruloplasmin, serum copper and urinary copper were normal. Antinuclear antibodies (ANA) were positive at 1/160 speckled in appearance. Anti-smooth muscle antibodies (anti-SMA) was positive at 1/120. Anti-SLA (Soluble Liver Antigen), anti-LKM1 (Liver-Kidney-Microsome type 1) and native anti-DNA antibodies were negative. A liver biopsy was recommended but not available. The aggregate score without treatment calculated from laboratory studies was 16 points indicating definite AIH (Table 1). Type I AIH was retained on clinical-biological, radiological and immunological criteria. The chest X-ray was normal (Image 1b). Blood cultures and cyto-bacteriological examinations of urine were negative. Trial corticosteroid therapy (Prednisone?) at an initial dose of 1 mg/kg/day was started on 06/15/2018, for a period of 8 weeks followed by a reduction. Azathioprine (Imurel?) at a dose of 2 mg/kg/day was introduced 2 months after the start of corticosteroid therapy (08/19/2018). The combination corticosteroid therapy and azathioprine were well tolerated. Laboratory assessment after 8 weeks of treatment showed marked improvement in cytolysis with normalization of transaminases. The aggregate score with treatment was 18 points (Table 1). The diagnosis of type I AIH was

maintained. In addition, a second search for anti-tissue antibodies was carried out on 12/23/2018 reporting positive anti-SMA, confirmed our diagnosis of type I AIH. At 18 months of treatment (12/12/2019), the liver function tests remained normal. The combination therapy was continued.

Case 2

A 39-year-old man of Malagasy origin was seen on an outpatient basis in August 2018 for progressive worsening jaundice with dark urine and discolored stools. The patient had no specific pathological history. He did not report drug addiction, hepatotoxic drugs and viral contagion. The physical examination found frank conjunctival jaundice. The patient is well aware, without hepatomegaly and without ascites. No signs of advanced liver disease and signs of heart failure were detected. Laboratory examinations reported ALT at 1590 (< 45) IU/L, AST at 983 (< 35) IU/L, PAL at 387 (53-128) IU/L, γGT at 960 (< 55) IU/L, total bilirubin at 175 (< 20) µmol/L, conjugated bilirubin at 134 (< 9) µmol/L, albuminemia 33 (40.20-47.60) g/L, serum ferritin at 1700.42 (21.81-274.66) ng/mL, γ-globulin at 26 (8-13.5) g/L and prothrombin level at 60% (70-100) with INR at 1.2 (0.80-1.30). Abdominal ultrasound showed normal liver parenchyma without focal lesions, absence of bile ducts dilation and absence of intrahepatic lithiasis (Image 2a). Hepatitis viral markers A, B, C and E were negative. The anti-tissue antibodies (ANA, anti-SMA, anti-LKM1, anti-SLA, anti-mitochondria type M2, native anti-DNA) were all negative. The serum transferrin saturation, serum ceruloplasmin, serum copper and urinary copper were normal. Liver biopsy was strongly recommended but not available. The aggregate score without treatment calculated from laboratory examinations was 11 points indicating probable AIH (Table 1). Acute autoimmune seronegative hepatitis has been suspected. The chest X-ray was normal (Image 2b). Blood cultures and cytobacteriological examinations of urine were negative. Trial corticosteroid therapy (Prednisone?) at an initial dose of 1 mg/kg/day was started, for a period of 8 weeks followed by a reduction. Normalization of transaminases was obtained after 8 weeks of treatment. Corticosteroid therapy was stopped due to side effects. Monthly follow-up has recommended. A progressive increase in transaminases was been demonstrated with respective levels of ALT and AST at 3xULN and 1.7xULN at 2 months then 6.5xULN and 4.2xULN at 3 months, motivating the resumption of corticosteroid therapy. The aggregate score with treatment was 16 points indicating Probable seronegative AIH (Table 1). Azathioprine (Imurel?) at a dose of 2 mg/kg/day was introduced one month after resumption of corticosteroid therapy. The combination corticosteroid therapy and azathioprine were well tolerated. A second search for anti-tissue antibodies was carried out in October 2019. The anti SMA, LKM1, anti-mitochondria type M2, native anti-DNA remained negative. ANA and Anti-SLA were positive with a respective rate of 1/160 and 1/80. The final diagnostic score was 21 points indicating a definite type 1 AIH (Table 1). The reassessment in November 2019 and January 2021 showed a good general condition and persistence of the normalization of transaminases, gamma globulins signing a prolonged remission. The combination therapy has been continued and discontinuation of treatment is probably impossible in the absence of a biopsy.

DISCUSSION

We report two cases of AIH including one case of type I AIH and a case of seronegative AIH finally classified as type I AIH. Our objective is to show through these different forms of AIH reported and the investigations available to Madagascar, the difficulty in making the diagnosis and taking charge of this disease in low-income countries and encouraging our neighboring colleagues who are in a similar situation. The unavailability of liver biopsy plays a major role in this difficulty, but should never constitute an obstacle in terms of autoimmune liver disease.

Type I AIH is the most frequent form (80% of cases), characterized by the presence of ANA (50-70% of cases) and/or SMA (85% of cases) in the typical forms or the presence of anti-SLA antibodies (6-32%) in the atypical forms. While seronegative AIH (10%) represent the particular forms of AIH.[7-9] Acute hepatitis with an ALT level of > 10xULN was the mode of revelation of our two observations. This shape represents 25 to 30%.[7]

The diagnosis of AIH can be confirmed by simple diagnostic criteria associating the absence of other causes, the presence of autoantibodies at a significant level, γ-globulins [?] 1.5xULN and interface hepatitis on liver

biopsy.[2, 7-10] Viral hepatitis (HAV, HVB and HVD, HVC, HVE, CMV, HSV, EBV), drug-induced hepatitis, Wilson's disease, non-alcoholic steatohepatitis, hemochromatosis, chronic alcoholism, α1-antitripsin deficiency, primary biliary cholangitis and primary sclerosing cholangitis are the main differential diagnoses.[4-10] Elimination of the latter remains a very important step in retaining the diagnosis of AIH. Histology showing suggestive lesions (interface hepatitis with lymphoplasmacytic infiltrates) is a mandatory component of the diagnosis.[7-10] Lack of histology remains a barrier to diagnosing AIH in low-income countries, where liver biopsy is not always available. Yet the other criteria, when considered collectively, have a very strong positive predictive value for the diagnosis of AIH; taken separately, none are specific, justifying the proposal for an AIH diagnostic score by the International Autoimmune Hepatitis Group (IAHG). The total score gives an assessment of the likelihood of a certain or probable AIH diagnosis. The overall sensitivity for a definite or high probability diagnosis of AIH is approximately 90%.[2, 7-10] In Madagascar, the diagnosis of AIH is still a challenge. Liver biopsy is not yet available to everyone. The cost of laboratory tests is luxurious for most patients. Systematic use of diagnostic score and test corticosteroid therapy becomes essential. Therefore, we retained the diagnosis of AIH in our observations on bundles of arguments associating the absence of other differential diagnoses, certain or probable diagnosis after the revised AIH score without histology, a complete response or relapse during a trial corticosteroid therapy.

AIH is the first chronic liver disease to have benefited from a medical treatment with proven efficacy on survival.[4-6] All recent guidelines propose first-line corticosteroids (up to 60 mg/day) whether or not associated with azathioprine (1 to 2 mg/kg/day). Early initiation of azathioprine is strongly recommended in order to limit the side effects of corticosteroids.[2, 4-6] EASL recommends initiation of azathioprine two weeks after administration of corticosteroids.[4] Budesonide ± azathioprine is preferable for non-cirrhotic patients. This association is the source of a significant remission rate after 6 months of treatment.[11] Our two patients were put on corticosteroids and azathioprine. The introduction of azathioprine was delayed in our patients due to diagnostic uncertainty requiring initial trial corticosteroid therapy as monotherapy. This makes it possible to objectify a non-response and rule out hepato-toxicity to azathioprine later. All our patients were symptomatic with ALT $>$ 10xULN justifying our decision to start treatment because they had formal therapeutic indications according to the current guidelines (BSG and AASLD).[5, 7] The therapeutic efficacy is judged on clinical and biological criteria (disappearance of symptoms, reduction or even normalization of transaminases and γglobulins). Complete remission was defined by absence of symptoms, normal concentrations of bilirubin and γ-globulins, transaminases less than 2xULN and normal or mildly inflammatory liver histology.[4-6, 8-10]Discontinuation of treatment may be considered in the event of prolonged biological remission [?] 2 years, if possible [?] 4 years without corticosteroid dependence, absence of cirrhosis, absence of previous relapse, absence of residual histological inflammation and absence of progression of fibrosis on liver biopsy.[4-6, 12]Kanzler et *al* in 2001 suggested that treatment for more than 4 years increased the chances of prolonged remission compared to treatment for 2 years.[12] A liver biopsy is essential before stopping treatment because the level of residual inflammation is a factor for relapse.[13] At two months of treatment, our two of the patients had complete remission. If treatment is stopped, regular biological monitoring(transaminases) could be carried out every month for 4 to 6 months and then every 3 months. This makes it possible to quickly detect a relapse.[7-10]

CONCLUSION

These were the first descriptions of AIH cases in Madagascar. AIH is a diagnostic challenge in low-income countries, requiring the use of diagnostic score and initial trial corticosteroid therapy. In two observations, the diagnostic of AIH was retained on clinical, biological, radiological and immunological arguments. Autoimmune liver disease is a real problem in low-resource countries. Therefore, a large-scale study on a Malagasy population seems necessary taking the epidemiological, therapeutic, prognostic aspects.

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CONFLICT OF INTEREST

None declared.

AUTHORS CONTRIBUTIONS

CIR were the main contributors to drafting the manuscript. ALRR contributed to study design, diagnosing the disease and performed the final manuscript. BMR contributed to literature search, data collection and figure preparation. MR, HDL, ASR, THR, SHR and RMR performed the final manuscript. All authors have read and approved the manuscript.

ETHICS STATEMENT

This was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Published with written consent of the patient.

DATA AVAILABILITY STATEMENT

Data available on request from the corresponding author.

REFERENCES

1. Jemilohun AC, Adewoye OG. liver cirrhosis from autoimmune hepatitis in a Nigerian woman: a case report. *Ann Ibd. Pg. Med.* 2017; 15 (2): 133-136.
2. Chazouillère O. A case of auto-immune hepatitis. Gastroenterol*Clin Biol* 2009; 33: 36-43.
3. Jemilohun AC, Ola TS. Autoimmune Liver Diseases in Native Black Africans: Extremely Rare or Inadequately Investigated Diseases?*JAMMR.* 2017; 24(7): 1-14.
4. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol.* 2015; 63: 971-1004.
5. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* . 2011 :1-19.
6. Mack CL, Adams D, Assis DN, et al. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines from the American Association for the Study of Liver Diseases. *Hepatology* . 2020; 0(0): 1-52.
7. Corpechot C, Chazouilleres O. autoimmune hepatitis: Diagnostic and therapeutic up-to-date. *Rev Med int.* 2010; 13: 606-14.
8. Lemoinne S, Wendum D, Corpechot C, Chazouillères O. Hépatites auto-immunes : aspects diagnostiques et thérapeutiques. *Hépato Gastro.* 2016 ; 23 : 637-52. doi : 10.1684/hpg.2016.1323.
9. Gournay J. L'hepatite auto-immune. *Hépato Gastro.* 2017; 24: 830-845. doi : 10.1684/hpg.2017.1521.
10. Manns MP, Strassburg CP. Autoimmune hepatitis: clinical challenges.*Gastroenterology.* 2001; 120: 1502-17.
11. Manns MP, Bahr MJ, Woynarowski M, et al. Budesonide 3 mg tid is superior to prednisone in combination with azathioprine in the treatment of autoimmune hepatitis. *J Hepatol* . 2008; 48: S369-70.
12. Kanzler S, Gerken G, Lohr H, et al. Duration of immunosuppressive therapy in autoimmune hepatitis. *J Hepatol* . 2001; 34:354-5.
13. Czaja AJ, Davis GL, Ludwig J, Taswell HF. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. *Hepatology* . 1984; 4: 622-7.

Variables (points)

1) Sex, Female (+2)
2) Immune disease (Thyroiditis, colitis, others) (+2)
3) Drugs, Positive (-4) / Negative (+1)
4) Alcohol, > 60 g/d (-2) / < 25 g/d (+2)
5) Viral markers, Negative (+3) / Positive (-3)

Variables (points)
6) γ-γλοβυλιν ορ ΙγΓ λεελ, > 20 g/l (+3) / 15-20 g/l (2) / 10-15 g/l (+1) / <10 g/l (0)
7) ALP/AST, < 1,5N (+2) / 1,5-3N (0) / > 3N (-2)
8) ANA, SMA, anti-LKM1 titers, >1:80 (+3), 1:80 (+2), 1:40 (+1), < 1:40 (0)
9) AMA positive (-4)
10) Histological features, Interface hepatitis (+3), lymphoplasmocytaire infiltrate (1), Rosette formation (1), None of th
11) Others markers (anti-SLA, Actin, LC1, pANCA) (+2), **HLA (DR3 or DR4)** (+1)
12) Aggregate score without treatment, Definite AIH (>15) / Probable AIH (10 à 15)
13) Treatment response, Complete (+2) / Relapse (+3)
14) Aggregate score with treatment, Definite (>17) / Probable AIH (12-17)
CT: Corticosteroid Therapy, ALP: Alkaline Phosphatase, AST: Aspartate Aminotransferase, ANA: antinuclear antibody, SM

TABLE 1: Diagnostic score according to IAHG 1999 and scores of our patients

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