Case Series

Childhood Autoimmune Hepatitis in Bahrain: a Tertiary Center Experience

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ABSTRACT

Background: Autoimmune hepatitis (AIH) in childhood has variable modes of presentation, and the disease should be suspected and excluded in all children presenting with symptoms and signs of prolonged or severe acute liver disease. In AIH, the liver biopsy histopathology shows inflammation in addition to presence of serum autoimmune antibodies and increased levels of immunoglobulin G (IgG). Objectives: To investigate the situation of childhood autoimmune hepatitis in Bahrain and to compare it with other studies worldwide. Methods: A retrospective study describing the AIH pediatric cases diagnosed during the period of Jan 2005 to Dec 2009. We report the clinical, biochemical, histopathological, and immunological findings, mainly autoimmune profile, in addition to response to treatment, of Bahraini children with autoimmune hepatitis. Results: Five Bahraini children, three females and two males were diagnosed as autoimmune hepatitis during the study period. Their ages at presentation ranged from 9 to 15 (median 10.6) years. One of our patients had a fulminating type. Two had other autoimmune related conditions, namely autoimmune sclerosing cholangitis and ulcerative colitis. All were AIH type 1. Variable response to conventional immunosuppressive therapy was found, from an excellent response with good prognosis, to cirrhosis, hepatic failure and liver transplantation. Conclusion: Childhood AIH is a rare medical problem in Bahrain, with both sexes affected and a variable response to immunosuppressive therapy.


Keywords: Autoimmune Hepatitis, Bahrain, Children
INTRODUCTION

Autoimmune Hepatitis (AIH) has a variable presenting picture in childhood, and the disease needs to be ruled out in all children with acute liver disease. In autoimmune liver disease the liver biopsy shows mainly inflammation, while the serum of the patient shows presence of autoimmune liver profile antibodies and increased levels of immunoglobulin G (IgG); other hepatic diseases need always to be ruled out. Immunosuppressive therapies, including corticosteroids are indicative in all types of childhood AIH; nevertheless patients with type I have a higher frequency of acute hepatic failure and relapse after stopping the steroids compared to patients with type II. The mean annual incidence of AIH among white, northern Europeans is 1.9 per 100,000 and its point prevalence is 16.9 per 100,000. Recent studies have documented that the incidence and prevalence of this disease have remained essentially unchanged over the last 2 decades. In Europe, the reported percentage of AIH among cases needing liver transplantations is 2.6% (1).

MATERIALS AND METHODS

The current study is the first in Bahrain to investigate childhood AIH and to compare it with other studies worldwide.

Patients and Laboratory Methods. A retrospective study reviewing the pediatric cases diagnosed as autoimmune hepatitis, during the period Jan 2005 to Dec 2009, in the biggest governmental hospital in the Kingdom (1000 beds) which is providing tertiary care to the entire island; approval from the hospital ethical committee was taken. The laboratory autoimmune profile, histopathological and clinical findings, in addition to response to treatment, of five Bahraini children among 50 studied cases, with autoimmune hepatitis is reported. Diagnosis was made according to the clinical and laboratory findings, including liver biopsy and serum autoimmune liver profile. Exclusion of other diseases that may show similar conditions was made whether of viral or metabolic etiology. Anatomical causes were ruled out by radiology, mainly MR cholangiography. Clinical history excluding drug consumption or other toxic materials was made. Hepatitis B virus, hepatitis C virus, Epstein-Barr virus and Cytomegalovirus were excluded by appropriate serologic tests.

Biochemical tests: serum ceruloplasmin, 24-hour urinary copper excretion, alpha-1 antitrypsin concentrations and alanine aminotransferase (ALT) were measured by automated chemical analyzer (Siemens, Munich, Germany).

Immunological tests: Antinuclear antibody test (ANA), was done by an indirect immunofluorescence assay (IFA) (Bio-Rad, Hercules, CA, USA) with positive more than or equal to 1:80 using Hep-2 cells; smooth muscle antibody (SMA), anti-mitochondrial antibody (AMA), and liver-kidney-microsomal antibody (LKM-1) were tested at a dilution of 1:10 by indirect immunofluorescence assay (IFA) (Bio-Rad, Hercules, CA, USA); serum immunoglobulin IgG concentrations were measured by the nephelometry method using a BN Systems nephelometer (Siemens, Munich, Germany). All laboratory methods used had positive and negative controls, in addition to internal controls and instruments calibrators.

Histopathology tests: Liver biopsies were reported using histopathology criteria described elsewhere (2).
Table 1. Clinical characteristics of the studied AIH patients (n=5).

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>12 y</td>
<td>11 y</td>
<td>9 y</td>
<td>10 y</td>
<td>11 y</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td>Jaundice + dark urine colour + pigmentation on neck &amp; elbow</td>
<td>Icteric look + nausea &amp; vomiting 12-15 times/day + abdominal pain</td>
<td>Jaundice + change colour urine and stools</td>
<td>Jaundice + dark urine</td>
<td>Jaundice + change urine colour + loss of weight + diffuse abd. Pain</td>
</tr>
<tr>
<td>Family history</td>
<td>3 uncles dies with same condition</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Associated clinical disease</td>
<td>Oesophagealvarices G6PD anaemia</td>
<td>-Ulcerative colitis- Sclerosing cholangitis</td>
<td>Nil</td>
<td>Aplastic anaemia</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Immun. suppressive therapy</td>
<td>Steroids + Azathioprine</td>
<td>Steroids + Azathioprine</td>
<td>Steroids + Azathioprine</td>
<td>Steroids + Azathioprine</td>
<td>Steroids + Azathioprine</td>
</tr>
<tr>
<td>Response/Outcome</td>
<td>Good</td>
<td>Hepatic failure → liver transplant → death</td>
<td>Good</td>
<td>Good</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Table 2. Laboratory findings of the AIH studied cases (n=5).

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Alk. phosph.</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>SGPT</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Globulins</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>IgG</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>Weak positive</td>
</tr>
<tr>
<td>ASA</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>positive</td>
</tr>
<tr>
<td>LKM</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>AMA</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td><strong>Liver biopsy histopathology</strong></td>
<td>Chronic active hepatitis + cirrhosis</td>
<td>Sclerosing cholangitis + cirrhosis</td>
<td>Autoimmune hepatitis Mild fibrosis No cirrhosis Spotty necrosis</td>
<td>Not done</td>
<td>Auto immune hepatitis with inflammation and fibrosis</td>
</tr>
</tbody>
</table>
RESULTS

Clinical features including presenting signs and symptoms, autoimmune profile, associated diseases and response to therapy are summarized in Table 1 while liver biopsy and laboratory findings are in Table 2. Only five Bahraini children, three females and two males were diagnosed as autoimmune hepatitis during the studied period. Their ages at presentation ranged from 9 to 15 (median 10.6) years. One of our patients had a fulminating type. Two had another clinical illness namely sclerosing cholangitis and ulcerative colitis (overlap syndrome) in one and hypothyroidism in another. All were AIH type 1. Variable response to conventional immunosuppressive therapy was found, from an excellent response with good prognosis, to cirrhosis, hepatic failure and liver transplantation.

DISCUSSION

The prevalence of AIH in Bahrain is not known whether in childhood or among adults; the literature on the subject is scarce from the Middle East.

In Saudi Arabia as an example of a nearby Arabian country, two studies reported data on AIH, one of them reviewed 112 liver transplant patients, 14.3% were initially suffering from AIH (3), while the other reported findings of 41 patients with AIH (4). A study from Iran reported that AIH constituted 5.6% of their total childhood liver disease (5), while in India, some studies reported 3.5%-6.1%, (6,7) which is less than the figures reported from North America and Europe which is 11%-23% (8), and reports from Brazil which are 5%-10% (9).

In our study the ages ranged from 9 to 15 (median 10.6) years; while in a study from Iran, the median age was reported to be 8.4 (range 3-13) years (5) and in a study from Turkey the age ranged from 7 to 14 years (10). In the current study both sexes were present with female to male ratio 3:2, while a study from Egypt reported a ratio of 2.3:1 (11). Other studies in Iran, Brazil and Europe reported a female predominance (5,9,12); similarly, in a study from Saudi Arabia the female predominance 75.7% was reported (4).

All our patients (100%) had acute hepatitis at presentation; this is in contrast to the published figures in the adult form of the disease which ranged from 13.1% in a study from India (6) to 36.4% in a study from Saudi Arabia (4) while in western countries it ranged from 26% to 40% (13,14). None of our reported patients were asymptomatic; other studies reported that asymptomatic patients had lower serum ALT versus symptomatic patients (4,15).

Regarding the severity and the disease advancement, only one of our patients (20%) had a fulminate disease. A study from Iran reported that 3% of the studied cases had fulminant hepatic failure while 13% had acute liver disease (5). In the adult AIH, a study from Saudi Arabia reported that 50% of their young patients had decompensated cirrhosis at presentation (4), and a study from India reported 34.2% (6). Some studies reported that older patients had more advanced disease (16,17).

In the current study all the children had increase in the liver enzymes; similar findings were reported in other studies (10,11).
Laboratory autoimmune profile namely anti-smooth muscle antibodies, anti-mitochondrial antibodies, and antibodies to LKM, in addition to antinuclear antibodies are the main serologic markers for autoimmune hepatitis. Those tests are not by themselves diagnostic for the disease; yet being positive narrows the differential diagnosis and helps in AIH classification (11,18). All of our patients had positive ASM antibodies (100%), while LKM and AMA were negative in all the cases. Three cases (60%) had positive ANA, while a study from Saudi Arabia reported 87.8% positive ANA and positive SMA in 72.7% (4), on the other hand Czaja reported 67% for ANA and SMA together (19).

All our patients were found negative for LKM-I thus classified as type I AIH; similar findings were reported in other studies in Iran, Saudi Arabia, Brazil, and Europe (4,5,12,20); others found 4 to 20% of their patients having type II with positive LKM 1 (13). Elevated serum IgG has been reported to be the best diagnostic predictor for AIH as published in the “simplified criteria for the diagnosis of AIH” by Hennes and colleagues (21). All our patients had high IgG while in the Saudi cohort, serum IgG level was elevated in 61.5% of the patients (4).

Four of our patients had liver biopsy; three of which (75%) had typical histological features of AIH based on the AIH scoring system (22). In a study from Iran, 90% had typical histological findings of AIH (5). Liver biopsy, although an invasive method, is necessary to establish the diagnosis. The typical histological features are: dense infiltration of the portal areas with mononuclear and plasma cells, expanding into the liver lobule; the hepatocytes at the periphery of the lobule being destructed, in addition to erosion of the limiting plate, known as “interface hepatitis”; collapse of the connective tissue due to death of the hepatocyte and expansion from the portal area into the lobule, known as “bridging collapse” and hepatic regeneration with “rosette” formation (1). Thus the main histological findings are interface (preseptal or perioral hepatitis with lymphoplasmatic necroinflammatory, with or without lobular (intra-acinar) involvement, central-portal or porto-portal bridging necrosis with liver cell rosettes formation and many plasma cells (11,20) In previous studies, cirrhosis was reported in variable percentages ranging from less than half reaching more than 90% of AIH children (20,23,24). In the current study, two of four cases (50%) had cirrhosis. In a study from Egypt on 11 children, histological findings showed interface hepatitis in all, while 54% had fibrosis and 27% had cirrhosis (11). Another study (25) reported that 36% of the initial biopsy of the studied AIH children, before treatment, showed cirrhosis.

In the current study, one of our cases was associated with primary sclerosing cholangitis, thus to be considered as overlap syndrome; she had also ulcerative colitis. This child had hepatic failure, which indicated liver transplantation but she deteriorated and died subsequently. In a study from Iran (5), autoimmune sclerosing cholangitis was rarely observed.

In a large 16 year retrospective study in UK, reported that AIH and autoimmune sclerosing cholangitis are similarly prevalent in children and are likely to belong to the same disease process (12).

One of our cases (20%) had hypothyroidism. Autoimmune thyroiditis is the most common autoimmune disease associated with AIH. Older AIH patients were found to have more often coexisting autoimmune disorder (17). In a study from Saudi Arabia on adult autoimmune hepatitis, 18% had coexisting autoimmune disease (4) as SLE, rheumatoid arthritis, Hashimoto’s thyroiditis.
Patients with established cirrhosis were more common to have failure of the treatment and the prognosis is related to the histological severity; with treatment failures occurring in general for about 20% of patients with AIH (26). In a study from Turkey, two patients who died were those with cirrhosis in the initial biopsy in addition to portal hypertension (10). Only one of our patients had treatment failure (20%), with liver transplantation and death, the rest (80%) had good treatment response. Our result is similar to that reported internationally for complete response, which is 65% at one and a half years and 80% at three years (13). Fulminant forms of AIH in un-transplanted patients have high mortality rate (27).

We agree with others in that the scoring system proposed by the International Autoimmune Hepatitis Group (22), can be used in the pediatric age group (5,28). Genetic factors play a role in the disease severity of AIH (29). In the present study, one of our cases had three uncles who died from similar conditions. Professor Mieli-Vergani from King’s College hospital, UK wrote in his recent review article on AIH, published 2013: ‘A deeper understanding of the pathogenesis of autoimmune liver disease will contribute to the development of novel treatment aimed at the restoration of tolerance to the liver derived antigens’(30). Indeed this is the hope for future immunotherapy in order to hopefully achieve immune tolerance.

Childhood AIH is a rare medical problem in Bahrain, with both sexes affected and with a variable response to immunosuppressive therapy. The small number of patients reported in the current study is considered a limitation and the need of a multicenter national data including pediatric and adult cases is recommended.

ACKNOWLEDGEMENTS

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REFERENCES