

Autoimmune liver disease in Asian children

Giorgina Mieli-Vergani · Diego Vergani

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Juvenile (i.e. affecting children and adolescents) autoimmune liver diseases are progressive inflammatory liver disorders that include autoimmune hepatitis and autoimmune sclerosing cholangitis.

Autoimmune hepatitis (AIH) is characterized serologically by high levels of transaminases and immunoglobulin G (IgG), as well as presence of autoantibodies, and histologically by interface hepatitis, in the absence of a known etiology [1]. Three fourths of patients are girls, some 20 % have associated autoimmune disorders—including thyroiditis, vitiligo, type 1 diabetes, inflammatory bowel disease, IgA nephropathy—and about 40 % have a family history of autoimmune disease [2]. In children and adolescents, AIH has a more aggressive course than in middle-age and elderly patients and often presents acutely, though its mode of presentation is very variable, and the disease should be suspected and excluded in all children with symptoms and signs of liver disease not ascribable to more common pathologies. If diagnosed early, AIH responds satisfactorily to immunosuppressive treatment, which should be started as soon as possible, as if left untreated, AIH progresses rapidly to cirrhosis and liver failure. The disease course is often fluctuating, with flares and spontaneous remissions, a pattern that may unfortunately result in delayed referral and diagnosis. The majority of children, however, on physical examination have clinical signs of an underlying chronic liver disease (e.g. spider nevi, palmar

erythema, leukonychia, striae), firm liver and splenomegaly. Moreover, at ultrasound imaging, the liver parenchyma is often nodular and heterogeneous.

The epidemiology of childhood AIH is unknown, but AIH type 1 (AIH-1) [anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA) positive] accounts for 2/3 of the cases and presents often around puberty [2], whereas AIH-2 [positive for anti-liver kidney microsomal antibody type 1 (anti-LKM1) and/or anti liver cytosol type 1 antibody (anti-LC1)] tends to present at a younger age and also during infancy. IgG is usually raised at presentation in both types, though 15 % of children with AIH-1 and 25 % of those with AIH-2 have normal levels. IgA deficiency is common in AIH-2 [2]. Severity of disease is similar in the two types, but anti-LKM1-positive children usually have higher levels of bilirubin and transaminases at presentation than those who are ANA/SMA-positive and present significantly more frequently with fulminant hepatic failure [2]. Excluding children with the fulminant presentation, a severely impaired hepatic synthetic function (prolonged prothrombin time and hypoalbuminaemia) is usually more common in AIH-1 than in AIH-2. The severity of interface hepatitis at diagnosis is similar in both types, but cirrhosis on initial biopsy is more frequent in AIH-1 than in AIH-2, suggesting a more chronic course of disease in the former. Progression to cirrhosis during treatment is more frequent in AIH-1.

In pediatrics, sclerosing cholangitis is often associated with florid autoimmune features, including elevated titres of autoantibodies, in particular ANA and SMA, elevated IgG, and interface hepatitis [3]. This AIH/sclerosing cholangitis overlap syndrome, called autoimmune sclerosing cholangitis (ASC) has been reported in between 15 and 21 % [4, 5] of patients in retrospective pediatric autoimmune liver disease series, where bile duct imaging was

G. Mieli-Vergani (✉)
Paediatric Liver, GI and Nutrition Centre, King's College
Hospital, Denmark Hill, London SE5 9RS, UK
e-mail: giorgina.vergani@kcl.ac.uk

D. Vergani
Institute of Liver Studies, King's College Hospital, Denmark
Hill, London SE5 9RS, UK

performed only in the presence of histological and/or biochemical evidence of biliary disease. However, in the only prospective study performed to date to our knowledge, aiming at establishing whether bile duct damage is present at disease presentation in children with features of autoimmune liver disease, ASC was found to have the same prevalence as AIH. In this prospective study, conducted over a period of 16 years and with a current follow up of 30 years, all children with serological (i.e. positive auto-antibodies, high IgG levels) and histological (i.e. interface hepatitis) features of autoimmune liver disease underwent a cholangiogram at the time of presentation, irrespective of their biochemical and/or histological findings [3]. Approximately 50 % of the patients enrolled in this prospective study had alterations of the bile ducts characteristic of sclerosing cholangitis and were diagnosed as having ASC. A quarter of the children with ASC, despite abnormal cholangiograms, had no histological features suggesting bile duct involvement, and the diagnosis of sclerosing cholangitis was only possible because of the cholangiographic studies. Virtually all ASC patients were seropositive for ANA and/or SMA. ASC was diagnosed in a similar proportion of boys and girls.

AIH and ASC have a similar mode of presentation, similar biochemical and immunological parameters, similar family history of autoimmune diseases and similar frequency of associated autoimmune disorders. However, inflammatory bowel disease, often asymptomatic or paucisymptomatic, is present in a higher proportion of patients with ASC (45 %) than with AIH (20 %). At the time of presentation, standard liver function tests do not help in discriminating between AIH and ASC, though the alkaline phosphatase/aspartate amino transferase ratio is significantly higher in ASC. Atypical perinuclear anti-neutrophil cytoplasmic antibody (atypical pANCA, also termed pANNA) is present in 3/4 of patients with ASC compared with 45 % of patients with AIH-1 and 11 % of those with AIH-2 [3].

Most series of juvenile autoimmune liver disease published to date comprise mainly Caucasoid patients [2–9].

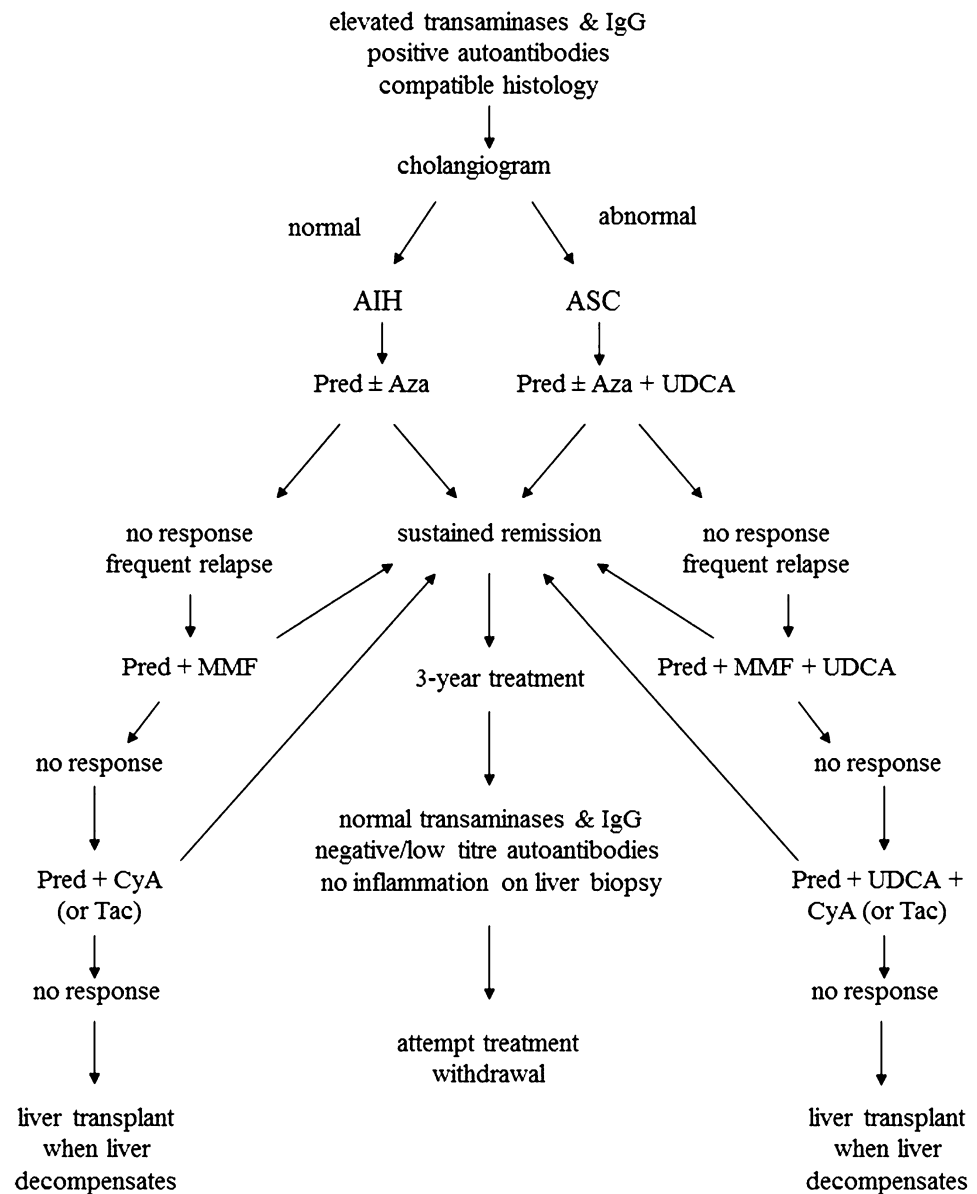
In the current issue of *Hepatology International*, Lee et al. [10] describe their experience on juvenile autoimmune liver disease in Malaysia. They report retrospectively 32 children of Malaysian, Chinese, Indian and Sabahan background referred to two pediatric centres, 18 with AIH-1, 5 with AIH-2 and 9 with ASC. This report is important as it shows that, contrary to what hitherto believed, juvenile autoimmune liver disease affects children of all ethnic backgrounds, including Asian children. In countries with a strong past or current history of epidemic viral hepatitis B, often the diagnosis of autoimmune liver disease has been overlooked, delaying lifesaving treatment.

The patients described by Lee et al. [10] have laboratory findings similar to those described in Caucasoid patients, a lower prevalence of family history of autoimmune disease (14 versus 40 %), a similar ~20 % association with autoimmune disorders—though among the Asian children there was a higher prevalence of systemic lupus erythematosus and a lower prevalence of inflammatory bowel disease, which, however, was investigated only when symptomatic and not routinely like in the UK prospective study [3]. In contrast to reports in Caucasoid patients, the Malaysian children appear to have a much worse prognosis, probably, as stated by the authors, because of the delay between first symptoms and starting treatment. Akin to previous reports in Caucasoid patients, a marked female preponderance was observed among Malaysian children with AIH-1 and AIH-2, while the majority of children with ASC were male. Such difference in gender confirms the findings of the UK prospective study [3].

A limitation of the report from Lee et al., due to its retrospective nature, is that cholangiographic studies were performed only in those children who had developed features of cholestasis (high conjugated bilirubin or gamma-glutamyl transpeptidase levels) during the course of the disease. This may have led to the diagnosis of AIH-1 in some children with bile duct disease at presentation, but absence of biochemical evidence of cholestasis. Unfortunately, the diagnostic scoring systems of the International Autoimmune Hepatitis Group (IAIHG), including the simplified one published in 2008 [11], while helpful in diagnosing autoimmune liver disease in children, do not allow discrimination between AIH-1 and ASC, as the two conditions are indistinguishable in the absence of bile duct imaging. The current recommendation for the differential diagnosis of juvenile autoimmune liver disease, therefore, is to perform a magnetic resonance cholangiogram at disease onset to differentiate between AIH and ASC, as the two conditions have a different prognosis [12] (Fig. 1). Thus, the UK prospective study shows that immunosuppressive treatment is effective in abating parenchymal inflammation and inducing biochemical remission both in AIH and ASC, but that in ASC bile duct disease tends to progress in about 50 % of cases despite treatment. In the absence of a cholangiogram at presentation it is possible that some of the Malaysian children diagnosed with AIH-1 did in fact have immunosuppression responsive ASC, as described in 50 % of the patients in the UK prospective study [3].

Lee et al. analyse prognostic parameters and identify a longer duration between first symptoms and initiation of treatment as the main factor linked to a poor outcome. Their data also indicate that a worse prognosis is associated to refusal of treatment or lack of adherence to therapy, 3

Fig. 1 Flowchart for treatment decision making in children with autoimmune liver disease. *AIH* autoimmune hepatitis, *ASC* autoimmune sclerosing cholangitis, *Pred* prednisolone, *AZA* azathioprine, *UDCA* ursodeoxycholic acid, *MMF* mycophenolate mofetil, *Tac* tacrolimus, *CyA* cyclosporine A [12]



out of 6 children dying without liver transplantation having these characteristics. Moreover, the report shows unequivocally that the prognosis of children with ASC is worse than that of children with AIH, 5 of the 9 patients with ASC dying or requiring liver transplantation over the 13-year observation period, compared to 3 out of 23 children with AIH. It would be interesting to know whether the 4 children with ASC alive and in remission include the 3 patients with small duct disease, a condition reported to have a better prognosis than ASC with larger duct involvement [13]. Of interest is that the time from first symptoms to beginning of treatment is longer in ASC than in AIH, probably as a result of a less acute and more frequently insidious mode of presentation of the former.

It would have been of interest to know how many of the Malaysian patients were positive for pANNA and for antibodies to soluble liver antigen (SLA), as anti-SLA, which is specific for autoimmune liver disease, is present in 30–40 % of the Caucoid patients with AIH or ASC at diagnosis [3] and is associated to a more severe disease course and a higher tendency to relapse [14].

In conclusion, the series of Lee et al. demonstrate that autoimmune liver disease affects children in Asia and that a much lower threshold of suspicion for AIH and ASC is needed in order to achieve a prompt diagnosis and proceed immediately to effective treatment. Early discrimination between AIH and ASC is important, as the two disorders are distinct, with different prognosis and

response to treatment. Most importantly, increased awareness of the clinical presentation and course of these disorders and of the necessity for early diagnosis and treatment among pediatricians and attending physician would be lifesaving.

Compliance with ethical requirements and Conflict of interest All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study. Giordina Mieli-Vergani and Diego Vergani declare that they have no conflict of interest.

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