Original paper

Classical autoimmune hepatitis and the IgG4-associated autoimmune hepatitis in paediatric patients

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The IgG4-associated autoimmune hepatitis (IgG4-AIH) is a newly proposed disease entity characterised by the accumulation of the IgG4-expressing plasma cells in the liver. Its pathophysiology and clinical significance remain unclear and have poor evidence in the paediatric population. Thus, our study aims at comparing the group of paediatric patients with classical AIH and the IgG4-AIH.
We carried out a retrospective analysis of 23 children (median age 8.5 years) diagnosed with AIH, who were compared according to the presence of IgG4-positive plasma cells in the liver biopsy.
IgG4-AIH was defined if 10 or more IgG4 positive plasma cells/high-power field were found in the biopsy.
The presence of the IgG4 component seems to be clinically insignificant. That is why, the conventional immunosuppressive protocol should be considered the standard treatment in the case of the IgG4-associated AIH.

Key words: autoimmune hepatitis, immunoglobulin G4-related diseases, children.

Introduction

Immunoglobulin G4-related diseases (IgG4-RDs) are systemic, chronic fibroinflammatory conditions characterised by a tissue infiltration with the IgG4-positive plasma cells, development of fibrosis and elevated serum levels of IgG4, mainly affecting men at 50–60 years of age. Among the children, the most affected organs are the orbit, salivary gland, pancreas, and lymph nodes. Hepatic involvement is less well established. There is still no certainty that the IgG4-autoimmune hepatitis (IgG4-AIH) is a subtype of AIH or rather a hepatic manifestation of IgG4-related diseases.

Material and methods

Our study aims at evaluating the frequency and characteristics of the IgG4-AIH in children in our hospital. We conducted a retrospective analysis of 23 paediatric patients with AIH diagnosed between 2011 and 2018. The diagnosis was based on the combination of clinical, biochemical, immunological, and histological features and the exclusion of other known causes of liver disease that may share serological and histological features with AIH. Twenty-one patients received the standard treatment consisting of prednisone and azathioprine, and 2 patients received only prednisone (the first of them was not treated with azathioprine because of the lack of antibodies and a slight inflammation in the liver biopsy, and the second because of a slight inflammation in the liver biopsy and low IgG concentration). Patients were divided into 2 subgroups according to the presence of IgG4-positive plasma cells in the liver biopsy. The IgG4-associated AIH was diagnosed if 10 or more IgG4-positive plasma cells/high-power field (HPF) were found in the liver biopsy (Fig. 1).

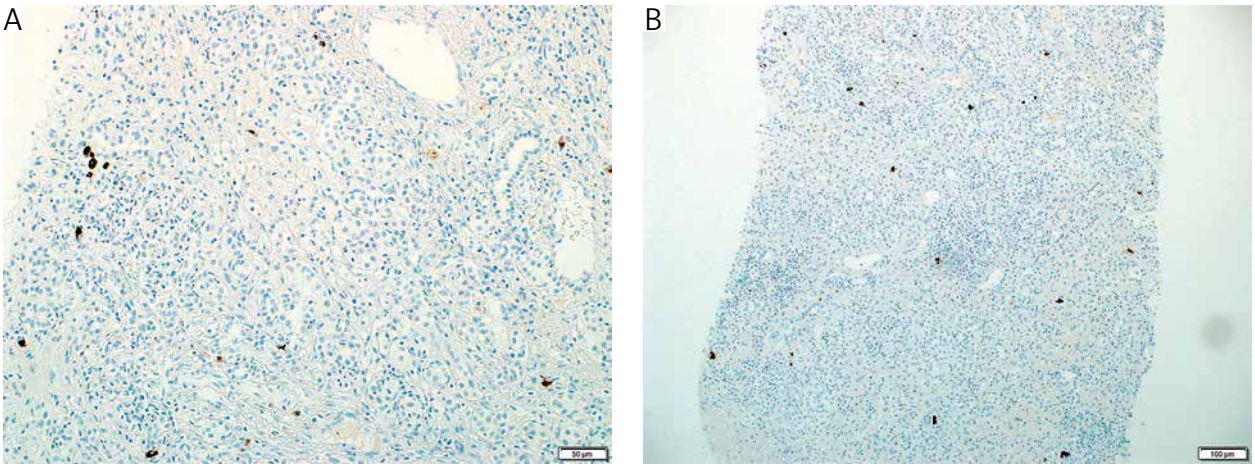

Fig. 1. IgG4-positive plasma cells in the liver biopsy

The control biopsy was proceeded after 25 months (on average). One patient did not have the control biopsy because of coagulation disorders.

Remission was defined as transaminase levels within the normal range, normalisation of IgG, either negative or lower (than at the moment of diagnosis) autoantibodies, and the histological resolution of inflammation or reducing the degree of inflammation.

Histopathology and immunohistochemistry

All liver biopsy specimens were fixed in 4% buffered formalin for 24 hours, embedded in paraffin blocks, and routinely stained by haematoxylin and eosin, periodic acid-Schiff with and without diastase, and Azan and Gomori silver to evaluate microscopic features. The histological interpretation was performed using internationally accepted criteria: the extent of inflammation (inflammatory infiltrates in portal tracts and lobules, interface infiltration) and fibrosis (portal and periportal fibrosis, portal to portal and portal to central septa), and was assessed by grade and stage based on the Batts and Ludwig scoring system. Additionally, plasma cell infiltration and lymphoid infiltrates between bile duct epithelial cells were assessed.

The phenotype of the inflammatory reactions was examined on paraffin-embedded tissue using monoclonal antibodies directed against IgG4 plasma cells by the EnVision system DAKO. IgG4-associated AIH was diagnosed if 10 or more IgG4-positive plasma cells/HPF were found in the biopsy. We then compared these 2 groups according to clinical and laboratory outcomes:

- grading,
- staging,
- portal inflammation grade,
- interface hepatitis grade,
- lobular hepatitis,
- bile duct damage,
- cholestasis.

Statistical methods

The statistical methods used in the study were the Mann-Whitney *U* test and Fisher's exact test.

Results

In our study, 23 paediatric patients were diagnosed with AIH (15 female and 8 male), average age 105 months. Eight patients (35%) satisfied the criteria of the IgG4-associated autoimmune hepatitis. Among the group 19 patients were type 1 AIH (6 patients with IgG4-associated AIH), 2 patients were type 2 AIH (a group with IgG4 associated AIH), and 2 patients were seronegative AIH (patients with classical AIH). There was no statistically significant difference between the clinical, laboratory, and histopathological findings between the groups (Table I). The grade and stage of the histopathological changes were measured by portal, interface and lobular inflammation, fibrosis, and bile duct inflammation.

Fifteen patients had magnetic resonance cholangiopancreatography, and only one patient had changes typical for primary sclerosing cholangitis (the patient had 0 IgG4 positive plasma cells in the liver biopsy). Seven patients (47%) in the group with AIH and 5 patients with the IgG4-associated AIH achieved remission, but there was no statistically significant difference in remission outcomes between these groups ($p = 0.17$) (Table II).

Discussion

To diagnose IgG4-related diseases we must satisfy these criteria: elevation of serum IgG4 concentrations and abundant infiltration of IgG4-expressing plasma cells [1]. On the other hand, IgG4-AIH is diagnosed based on significant accumulation of IgG4-expressing plasma cells in the liver biopsy [1]. There is still discussion about whether IgG4-AIH is a subtype

Table I. The clinical, laboratory, and histopathological characteristics of the study groups at the time of diagnosis

Parameters	Classical AIH (n = 15)	IgG4-associated AIH (n = 8)	Exact p-value
Age (months)	108 (48–168)	90 (30–144)	0.27
Gender [f/m]	9/6	6/2	0.66
Type 1 AIH	13	6	0.59
Type 2 AIH	0	2	0.11
Seronegative AIH	2	0	0.53
ALT [U/l]	423 (92–1587)	851 (162–2116)	0.32
AST [U/l]	422 (60–1696)	895 (93–3614)	0.48
GGTP [U/l]	110 (34–509)	67 (35–169)	0.16
IgG [g/l]	32.2 (10–47.8)	17.4 (13.6–32.6)	0.21
INR	1.25 (0.97–2.1)	1.37 (1.09–1.88)	0.67
Total bilirubin [mg/dl]	1.52 (0.22–19.07)	2.16 (0.40–7.57)	0.63
Grading	3 (2–4)	3 (2–4)	0.57
Staging	3 (0–4)	3 (2–4)	0.18
Portal inflammation grade	3 (2–4)	3 (2–4)	0.21
Interface hepatitis grade	3 (1–3)	3 (2–4)	0.30
Lobular hepatitis	2 (0–3)	2 (1–3)	0.65
Bile duct damage	1 (0–2)	1 (0–2)	0.47
Cholestasis y/n	3/12	1/7	0.99

Table II. The laboratory and histopathological characteristics of the study group at the time of control biopsy

Parameters	Classical AIH (n = 15)	IgG4-associated AIH (n = 7)	Exact p-value
ALT [U/l]	22 (7–248)	13 (8–472)	0.81
AST [U/l]	24 (15–150)	22 (17–320)	0.70
GGTP [U/l]	16 (9–238)	14 (10–57)	0.57
IgG [g/l]	13.4 (9.3–23)	9.9 (7.9–28)	0.23
INR	1.09 (0.94–1.26)	1.01 (0.98–1.17)	0.94
Total bilirubin [mg/dl]	0.56 (0.19–2.5)	0.31 (0.22–0.71)	0.06
Grading	2 (0–3)	1 (1–3)	0.52
Staging	2 (0–3)	2 (0–3)	0.80
Portal inflammation grade	2 (0–3)	1 (1–2)	0.43
Interface hepatitis grade	1 (0–3)	1 (0–3)	0.66
Lobular hepatitis	0 (0–2)	0 (0–2)	0.71
Bile duct damage	0 (0–2)	0 (0–2)	0.25
Cholestasis [y/n]	1/14	0/7	0.99

of classical AIH or it is rather a hepatic manifestation of IgG4-related diseases.

It is worth emphasising that in the literature we can find different criteria of IgG4-AIH, which is why the proportion of IgG4-AIH can be variable in different studies. For example, Chung *et al*. and Amarapurkar *et al*. defined the disease when in the liver biopsy there are minimum of 5 IgG4-positive plasma cells. In our work, we adopt the criteria used by Umemura *et al*. They proposed the diagnostic criteria for IgG4-AIH consisting of more than 10 IgG4-positive plasma cells/HPF. The same diagnostic criteria were adopted by Aydemir *et al*. They also reported the first study of IgG4-associated AIH in paediatric patients.

Most cases in the literature [2–6] reported that blood biochemical examinations do not distinguish

IgG4 AIH and IgG4 not associated AIH; we proved the same in our work.

Chunget *et al*, Umemura *et al*., and Canivet *et al*. reported no difference in serum ANA, but the IgG concentration was significantly higher in patients with IgG4-associated AIH in 2 studies: Chung *et al.* and Canivetet *et al*. [2, 3, 5]. In our study, we did not observe any statistically significant difference between levels of serum IgG and ANA titres.

By contrast to studies in adult AIH patients [2–5], the degree of chronic inflammation in children [6] did not show a significant difference between IgG4-associated AIH and IgG4-non-associated AIH, as judged by the grade of portal inflammation, interface hepatitis, rosette formation, and fibrosis. The adult patients with IgG4-related disease were characterised by a more advanced interface hepatitis and bridging fibrosis than the classical AIH patients [7]. In our work, in both the IgG4-positive and IgG4-negative groups we observed similar degrees of inflammatory changes and fibrosis stage. Also, we did not observe any difference in the severity of plasma cell infiltration in the portal areas, which is described in the IgG4-positive adult patients [8]. On the other hand, adult patients with IgG4 AIH are similar clinically and pathologically to classical AIH patients [9].

IgG4-AIH defined by Umemura *et al*. might be a hepatic manifestation of systemic IgG4-related disease. On the other hand, IgG4-AIH defined by Chung *et al*. might be a subtype of AIH characterised by moderately increased IgG4 responses in the liver, but not in the serum.

Storiform fibrosis is characteristic of IgG4-related diseases. Lack of multiple organ involvement as well as storiform fibrosis supports the idea that IgG4 AIH is a subtype of classical AIH rather than a hepatic manifestation of IgG4-related disease.

Conclusions

The presence of the IgG4 component confirms that among paediatric patients with autoimmune hepatitis, there are some cases with the type of AIH characterised by abundant infiltration of IgG4-positive plasma cells, but this component seems to be clinically insignificant. The conventional immunosuppressive protocol should be the standard treatment in the case of the IgG4-associated AIH.

We need more studies to decide if IgG4-AIH is a subtype of AIH characterised by abundant infiltration of IgG4-positive plasma cells in the liver biopsy, without the presence of IgG4 in the serum.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: Grant Zadanie Młodego Badacza M38/19.
4. Conflicts of interest: None.

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