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ORIGINAL ARTICLE

Mode of Presentation and Associated Autoimmune Diseases in Children with Autoimmune Hepatitis

Otoimmün Hepatit Tanılı Çocuklarda Başvuru Şekli ve Eşlik Eden Otoimmün Hastalik Varlığı

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ABSTRACT

Aim: Autoimmune hepatiti (AIH) is an inflammatory disease of the liver with variable clinical presentations. 20-40% of the patients with AIH had another associated autoimmune or autoinflammatory disease. This study aimed to assess mode of presentation, biochemical features and outcomes in children with AIH, as well as to evaluate the frequency of concomitant autoimmune diseases (CAIDs).
Materials and Methods: 17 children, aged 6 to 18 years were enrolled. The mode of presentation and accompanying autoimmune diseases were recorded. Biochemical parameters as well as immunoglobulin G levels were evaluated either at time of submission and thereafter.
Results: Fourteen patients had type-1AIH (10 females, 4 males), and three (2 males, 1 female) had type-2AIH. The mode of presentation was acute in 53% and incidental enzyme elevation in 47% of them. There was an associated autoimmune or auto-inflammatory disease in 35% of the patients, 12% had vitiligo, 6% had celiac disease, 6% had juvenile idiopathic arthritis, 6% had Familial Mediterranean Fever, and one patient had both type-1diabetes mellitus and Hashimoto thyroiditis (HT). The subjects with CAIDs were females (6 patients) with insidious type of presentation. Autoimmune diseases were observed in 24% of the parents (3 had HT, 2 had vitiligo).
Conclusion: AIH is a rare but important cause of chronic liver disease in children. Frequent association with autoimmune diseases should be kept in mind as the clinical expression of the associated disease can be extremely variable therefore diagnosis and treatment delay may occur.

Key words: Autoimmune hepatitis, child, extrahepatic autoimmune diseases

ÖZ

Giriş ve Amaç: Otoimmün hepatit (OİH)çocukluk çağında nadir görülen karaciğerin inflamatuar hastalığıdır. Klinik prezantasyon çok değişkendir. OİH olan hastaların yaklaşık %20-40'nda eşlik eden otoimmün hastalıklar gözlenebilir. Bu çalışmamızda OİH tanısı almış çocukların başvuru şekli, biyokimyasal parametreleri, eşlik eden otoimmün veya otoinflamatuar hastalık varlığının araştırılması amaçlanmıştır.
Gereç ve Yöntem: Yaşları 6 ila 18 arasında değişen, OİH tanısı almış 17 değerlendirildi. Başvuru şekli, laboratuvar bulguları, eşlik eden otoimmün veya otoinflamatuar hastalıklar, anne-babada otoimmün hastalık varlığı kayıt edildi. Biyokimyasal parametreler başvuru şekline ve eşlik eden otoimmün hastalık varlığına göre kıyaslandı.
Bulgular: OİH olan çocukların on dördü (10 kız, 4 erkek) tip1 OİH, üçü (1 kız, 2 erkek) ise tip-2OİH tanısı almıştı. Hastaların %53 akut hepatit, % 47 ise insidental karaciğer enzim yüksekliği nedeniyle başvurmuştu. OİH olan çocukların %35'inde eşlik eden bir veya birden fazla otoimmün veya otoinflamatuar hastalık gözlendi. En sık vitiligo (%12), ikinci sıklıkta ise Çölyak hastalığı (% 6) juvenil idiopatik artrit (%6), Ailevi Akdeniz ateşi %6 oranında gözlendi. Tip-1 OİH nedeniyle takip edilen bir hastada hem tip 1 diabetes mellitus hem de Hashimoto tiroiditi (HT) vardı. Eşlik eden otoimmün hastalığı olan çocukların hepsinin cinsiyeti kız ve insidental olarak enzim yüksekliği nedeniyle başvurmuş olanlardı. Hasta ebeveynlerinin % 24 de otiommün hastalık (üç kişide HT, iki kişide vitiligo) vardı.
Sonuç: Çocuklarda OİH, kronik karaciğer hastalığının nadir fakat önemli nedenleri arasındadır. OİH ile birlikte diğer otoimmün ve otoinflamatuar hastalıkların da eşlik edebileceği, erken tanının tedavinin gecikmemesi açısından önemli olduğu unutulmamalıdır.

Anahtar kelimeler: Otoimmün hepatit, çocuk, karaciğer dışı otoimmün hastalıklar vaskülarizasyon indeksi

Introduction

Autoimmune hepatitis (AIH) is a chronic, immune-mediated disease of the liver, characterized by elevated IgG levels and presence of specific autoantibodies. The inflammatory destruction of the liver tissue may consequently lead to cirrhosis and hepatic failure, making AIH the one of the leading causes of end-stage liver disease (1). The worldwide prevalence of AIH among patients with liver disease is between 11% and 20% (2). Due to its insidious presentation, the prevalence in the pediatric population is unknown however increasing incidence of the disease in children was reported (3,4). AIH is more frequent in female patients, with a female: male ratio of 3:1 (1,4). There are two types of AIH; type 1 (AIH-1),

defined by the presence of smooth muscle antibodies (SMA) and/or antinuclear antibodies (ANA), and type 2 (AIH-2), characterized by the presence of anti-liver/kidney microsome type 1 antibodies (LKM-1) (4). The SMA, ANA, and anti-LKM-1 are the serological markers of autoimmune hepatitis, and antibodies to mitochondria (AMA) are the serological hallmarks of primary biliary cirrhosis (PBC), however these serological features are not diagnostic, and other associated manifestations are necessary to establish the correct diagnosis (5). The clinical presentations of the disease are variable, from asymptomatic elevated levels of the liver enzymes to fulminant liver failure (1,2,3) Although acute hepatitis is the most frequent presentation in the pediatric age group, AIH usually has fluctuant course, partially explaining the delay between the first symptoms or signs and the diagnosis of the disease (6). Interestingly, in 20-40% of the adult patients, another concomitant autoimmune disease (CAID) such as thyroiditis, celiac disease, type 1 diabetes mellitus (DM type1), vitiligo, ulcerative colitis and mixed connective diseases were observed, either presented before, at the onset of the disease or later during the follow-up (1,5). However pediatric studies reported that CAIDs (excluding inflammatory bowel diseases) have been less frequently observed (7,8,9)

This study aimed to assess the mode of presentation, biochemical features and outcomes in children with AIH, as well as to evaluate the frequency of concomitant autoimmune disease in children with AIH.

Patients and Methods

This retrospective study consisted of 17 children, 6-18 years of age, with a definite diagnosis of AIH who were admitted to the Pediatric Hepatology Clinics between August 2014 and October 2021. The demographic and clinical features of the patients, and their laboratory, treatment and clinical outcomes were reviewed. The diagnosis of AIH was confirmed based on the scoring system of the International Autoimmune Hepatitis Group (10,11).

The presenting symptoms, physical evaluation, accompanying autoimmune disease and family history of associated diseases were recorded from the medical records. Routine laboratory tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total immunoglobulin G (IgG), total bilirubin and conjugated bilirubin, albumin, alpha fetoprotein (AFP), prothrombin time (PT), international normalized ratio (INR) and viral serologic tests for hepatitis A, B, C, Epstein–Barr virus, Cytomegalovirus, Parvovirus and Human Immunodeficiency Virus) were also recorded. Ultrasonographic evaluation of the liver parenchyma in case of chronicity was performed, and doppler ultrasound was used to exclude portal hypertension. Anti-smooth muscle antibodies (SMA), antimitochondrial antibodies (AMA), liver-kidney microsomal antibodies-1 (LKM-1), and antinuclear antibodies (ANA) were used as the serologic markers for autoimmune hepatitis (11). These antibodies, even not diagnostic, are useful for the classification of the disease (12). Serum ANA, SMA, AMA, and LKM-1 antibodies were studied by immunoblot assay and levels beyond 1/40 titer were considered "positive". Patients whose autoantibody levels were negative or ANA or SMA was positive were considered to have type 1 AIH and patients whose LKM autoantibody levels were positive were considered to have type 2 AIH. Levels of the immunoglobulin G(IgG) were screened either at the presentation and thereafter as elevated serum IgG has been reported to be the best diagnostic predictor for AIH (3,12).

All patients underwent a liver biopsy. Three of them had fulminant disease so the biopsy was performed during corticosteroid treatment after normalization of the coagulation parameters. Histopathological evidence of necro-inflammatory hepatocellular injury, portal mononuclear cell infiltration with plasma cells, parenchymal collapse was essential for the diagnosis of AIH. Inflammatory activity and fibrosis degree were evaluated using Ishak's histological activity index (13,14). Magnetic resonance cholangiopancreatography (MRCP) was performed to all patient with definite AIH diagnosis to exclude associated small bile duct pathologies (15). After AIH diagnosis was confirmed and treatment was started the patients were evaluated every two weeks in the first 2-3 months of treatment and every 3 months thereafter in uncomplicated cases (15). Remission induction and maintenance treatment, response, relapse, and drug side effects were collected from the patient charts.

Association of the AIH with other autoimmune and autoinflammatory disorders as well as autoimmunity in first degree relatives were recorded.

Methylprednisolone 2 mg/kg/day was started as a primary therapy for all patients. Azathioprine was added after 3-4 weeks of steroid treatment (15). All patients were tested genetically for Thiopurine methyltransferase (TPMT) mutations, to detect a TPMT deficiency. Azathioprine was switched to mycophenolate mofetil (MMF) in patients with side effects (3,15). Clinical and laboratory remission (aminotransferases, autoantibodies, and gamma globulin within normal limits) with negative autoantibodies (ANA, ASMA, anti-LKM-1) for at least 24 months was accepted as complete response to treatment (15, 16). The reactivation of the disease was considered when laboratory manifestations such as elevated aminotransferase levels, increased gamma globulin fractions, or the reappearance of autoantibodies were detected (15).

The study was approved by the local Institutional Ethical Board.

The results were analyzed by the Statistical Package for the Social Sciences (SPSS) version 22 for Windows (SPSS Inc.; Chicago, IL, USA). Shapiro Wilks test was

used to determine the distribution of the variables. The results were expressed as mean and standard deviation (SD) for normally distributed variables, while median and interquartile range for non-normally distributed variables. Independent samples t-test was used for comparison of normally distributed variables and Mann-Whitney U test was used for comparison of non-normally distributed variables. Related-samples Friedman's test was used for three groups of related variables and if difference was found pairwise comparison was applied to compare among groups. The comparison of two related groups was made with Paired-samples T-test for normally distributed, and Wilcoxon signed ranks test for non-normally distributed variables. Chi-square test was used for categorical variables. P values of less than 0.05 were accepted as significant.

Results

Seventeen children (11 females, 6 males), with a mean age of 11,57 (± 3,58) years, diagnosed with AIH were enrolled. The mode of presentation was acute hepatitis in 53% (29% with acute hepatitis, 24% with signs of fulminant hepatic failure) and incidental enzyme elevation in 47% of them. Fourteen patients (10 females, 4 males) had AIH-1 and three (2 males, 1 female) had AIH-2. There was an associated autoimmune or auto-inflammatory disease in six (35%) patients. All subjects with associated autoimmune disease were females (6 patients), two patients (12%) had vitiligo, one (6%) had celiac disease, one (6%) patient had juvenile idiopathic arthritis (JIA), one (6%) had Familial Mediterranean Fever (FMF), and one patient had both type 1diabetes mellitus (DM) and Hashimoto thyroiditis (HT). None of our patients had concomitant inflammatory bowel disease (IBD). Autoimmune diseases were observed in 24% of the parents of the children with AIH (three had HT, two had vitiligo).

At the diagnosis, mean weight standard deviation score (SDS) of the study group was 0.24 ± 0.85, mean height SDS was -0.49 ± 1.08, and mean body mass index SDS was 0.55 ± 0.93.

In the entire study group, hematologic parameters showed mild anemia in nine (53%) and moderate thrombocytopenia in two (12%) patients. Mean hemoglobin was 12.09±1.41 gr/dl, white blood cell count was 6932±1733/mm3, platelet count was 222.866 ± 56.553/mm3, median erythrocyte sedimentation rate was 23 mm/h. The median level of ALT at diagnosis was 558 (280-893) IU/L and AST was 382 (170-1134) IU/L.

The levels of ALT, GGT, total and conjugated bilirubin, INR were significantly higher in patients with acute or fulminant presentation compared to ones with incidental mode of presentation. Albumin was lower in patients with acute presentation. Total IgG, hemoglobin and platelet counts were not different (Table-1).

The comparison of anthropometric and biochemical parameters showed no difference among patients with isolated AIH and those with one or more associated autoimmune disease except a mild significance for INR (Table-2).

Elevated levels of all biochemical parameters decreased thereafter with appropriate treatment (Table-3).

Autoimmune profile of the children with AIH was as follows: ASM antibodies were positive in 58%of the patients, ANA in 82%, anti-LKM-1 in 18%, AMA in 12%, while p-ANCA positivity was observed in 35% of the cases (Table-4). The patients with strong ANA positivity were further evaluated regarding the differential diagnosis of Systemic Lupus Erythematosus (SLE). All liver biopsies were compatible with AIH. None of the patients had increased GGT and ALP levels. MRCP was performed to all patients, revealing no small or large bile duct involvement. Also, none of our patients had associated primary sclerosing cholangitis to be considered as overlap syndrome.

Methylprednisolone was the primary treatment protocol. No TPMT deficiency was detected consequently AZA was started to all patients, however two children were intolerant to it, accordingly they were switched to MMF.

The complete response to therapy had been achieved in all the patients except for one with AIH type2 who was non-adherent to treatment. He had two serious relapses presented as acute hepatitis, however he rejected to use medications regularly, therefore his enzyme levels as well as total IgG levels remained elevated. The reactivation of the disease was observed in 41% (7 children) of the patients, who were successfully treated with steroid dosage increment. None of the children was suitable for treatment discontinuation. There was no difference in term of response to treatment and rates of relapse between patients with incidental or acute presentation as well as between children with or without associated autoimmune or autoinflammatory disease.

Discussion

The present study revealed that children with AIH more frequently had concomitant autoimmune or autoinflammatory diseases than previously reported (6,7). The increased incidence of the IBD in children with AIH and PBS is well known, however AIH and other autoimmune disorder association was described less frequently (7,8). AIH may be associated with autoimmune disorders like thyroiditis, IBD, hemolytic anemia, vitiligo, celiac disease, insulin-dependent diabetes, Behçet's disease, idiopathic thrombocytopenia, and Addison disease, which were shown to exist in approximately 20% of the children (5,9,15). The exact frequency with exclusion of the IBD is not reported in children however studies from adult series showed that 10-20% of the patients with AIH had

concomitant autoimmune disease (CAID) (6,7,17). Previous studies reported that CAIDs tend to cluster in female patients with AIH-1 (17,18), accordingly in the current trial, all the children with CAIDs were females. Similarly recent trials from the Netherlands demonstrated that significantly more women with AIH had associated AID than men with AIH (19) which might be explained by hormonal variations, since both androgens and estrogens appear to inhibit and enhance immune activity (18). Past studies showed that the most common AIDs associated with type 1 AIH are autoimmune thyroiditis, type 1 diabetes and UC (7,18), whereas in the present study vitiligo was observed more frequently, fallowed by HT, type 1DM, Celiac disease, and FMF. Interestingly vitiligo was observed more frequently in patient with type 2 AIH (20), however in the present study one patient had type 1 and the other had type 2 AIH. Gregorio et al. published a 20-year follow-up work of pediatric AIH patients at King's College Hospital and reported that 20% of the patients had CAIDs, which included thyroiditis, vitiligo, type 1 diabetes and IBD (7). They also reported almost a similar frequency of CAIDs between children with type 1 AIH and type 2 AIH (7). Interestingly in a study from Argentina, children with AIH had lower frequencies of CAIDs compared to adults with AIH (13% vs 39%) (21). The authors suggested that the age increases the incidence of the development of CAIDs (21). However, the present study showed that in a pediatric population frequency as high as in adult series could be observed. Along with, children may present with syndromes associated with AIH (2,4). Therefore, children may also have AIH as a component of autoimmune polyendocrinopathy syndromes (APECEDs) (15). We had a one child with type 1 AIH, HT and type 1DM. Although she did not fulfil the criteria for APECED, she might develop the other associated diseases later in life (2,4). The diagnosis of the CAID is particularly important as prompt treatment should be initiated without delay (15).

Of note the frequency of autoimmunity was also increased in the first-degree relatives of the subjects with AIH (5,17,18). Gregorio et al reported a frequency as high as 40% in the relatives of the children with AIH (7). Although none of the first-degree relatives in our case series had AIH, 24% of the parents had autoimmune disorders.

In the current trial 81% of the patients had AIH type 1, whereas type 2 AIH was observed only in three patients, two of them boys. The previous studies both in children and adults reported that type 1AIH is more prevalent than type 2 (5,6). According to the previous pediatric studies, the female predominance was noted (8,9). Female to male ratio in children vary in different countries from almost equal in United States to 4:1 in South America and UK (8,9,15,19). The onset was usually uncharacteristic with chronic presentation predominating in adults, whereas pediatric reports as also in our study, showed that acute presentation is more prevalent (5, 9,15). Correspondingly in a trial from Argentina the acute viral hepatitis–like presentation was observed in 54% of adult AIH patients, which was significantly lower than the frequency observed in the children with AIH (54% vs. 70%) (**21**). Our patients with insidious mode of presentation were found to be more likely to have lower serum ALT compared to symptomatic patients (p 0.001). As expected, levels of total bilirubin and INR were increased in patients with acute onset. These results were like that reported by Feld et al. (22), who also noted that asymptomatic patients were older, however in the present study there was no age differences between acutely or insidiously presented subjects. Interestingly there were no differences among laboratory parameters

Table-1: Demographic, anthropometric, and biochemical parameters according to mode of presentation in children with AIH

	Incidental	Acute/Fulminant hepatitis	P
Age (mean ± SD) (years)	11.1 ± 3.50	12.0 ±3.81	0.432[a]
Sex (male/female) (n)	3/5	2/7	
Weight SDS	0.007 ± 0.71	0.508 ± 0.97	0.233[a]
Height SDS	-0.26 ± 0.95	-0.74 ± 1.24	0.650[a]
BMI SDS	0.26 ± 0.70	0.88 ± 1.09	0.261[a]
ALT (median (IQR)) (IU/L)	344.5 (165-464)	895.0 (638-1317)	0.001[b]
Total bilirubin (median (IQR) (mg/dl)	1.00 (0.64-1.51)	6.55 (1.93-8.42)	0.001[b]
Conjugated bilirubin (median (IQR) (mg/dl)	0.34 (0.13-0.75)	4.50 (0.64-6.84)	0.001[b]
GGT (median (IQR) (IU/L)	56.0 (23.7-117)	120.0 (56-124)	0.038[b]
Albumin (median (IQR) (g/dl)	4.20 (4.1-4.37)	3.30 (3.12-4.27)	0.037[b]
INR (median (IQR)	1.20 (1.1-1.38)	1.60 (1.21-1.85)	0.011[b]
IgG (median (IQR) (mg/dl)	2168 (1942-2514)	2607 (2165-5867)	0.080[b]
Platelet (mean ± SD) (/mm3)	246.250 ± 49.169	196.142 ± 55.496	0.191[a]
Hemoglobin (mean ± SD) (g/dl)	12.3 ± 1.02	11.8 ± 1.81	0.650[a]
Legend: SD, standard deviation; IQR: interquartile range; ALT, alanine aminotransferase, □-glutamyl transferase; IgG, immunoglobulin G; BMI: body mass index;			
INR, international normalized ratio			
* a: Independent samples T test (mean ±SD); b: Mann-Whitney U test (median (1st quartile-3rd quartile))			

Table-2: Demographic, anthropometric, and biochemical parameters according to the presence of associated autoimmune diseases in children with AIH

	No associated auto-immune disease	Associated autoimmune disease	P
Age (mean ± SD) (years)	11.6 ± 3.39	11.3 ± 4.35	0,651[a]
Sex (male/female) (n)	5/6	0/6	
Weight SDS	0.37 ± 0.91	-0.02 ± 0.73	0.269 [a]
Height SDS	-0.69 ± 1.14	-0.07 ± 0.90	0.687 [a]
BMI SDS	0.81 ± 0.82	0.03 ± 0.99	0.132 [a]
ALT (median (IQR)) (IU/L)	672 (386-891)	456 (230-1526)	0.763 [b]
Total bilirubin (median (IQR)) (mg/dl)	1.63 (0.96-5.91)	1.20 (0.72-8.25)	0.615 [b]
Conjugated bilirubin (median (IQR) (mg/dl)	0.70 (0.34-3.24)	0.80 (0.11-6.57)	0.580 [b]
GGT (median (IQR) (IU/L)	87.9 (49-120)	109 (27-138)	0.651 [b]
Albumin (median (IQR) (g/dl)	4.20 (3.35-4.40)	3.90 (3.25-4.15)	0.362 [b]
INR (median (IQR)	1.41 (1.19-1.74)	1.20 (1.09-1.30)	0.049 [b]
IgG (median (IQR) (mg/dl)	2433 (263-5822)	2197 (2062-2524)	0.447 [b]
Platelet (mean ±SD) (/mm3)	214.900 ± 55.322	238.800 ± 61.900	0.191 [a]
Hemoglobin (mean ±SD) (g/dl)	12.1 ± 1.64	11.9 ± 0.95	0.650 [a]
Legend: SD, standard deviation; IQR: interquartile range; ALT, alanine aminotransferase; GGT, □-glutamyl transferase; IgG, immunoglobulin G;			
INR, international normalized ratio			
* a: Independent samples T test (mean ±SD); b: Mann Whitney U test (median (1st quartile-3rd quartile))			

Table-3: Biochemical parameters at onset of the disease, 3 and 6 months after treatment in patients with AIH.

Parameter	At onset	3rd month	6th month	P*
ALT (median(IQR)) (IU/L)	558 (280-893)	51 (29-81)	24 18-43)	0.000 [a]
AST (median(IQR)) (IU/L)	382 (170-1134)	53 (46-63)	26 (20-32.5)	0.000 [a]
ALP (median(IQR)) (IU/L)	165 (98-261)	123 (76-157)	80 (74-129)	0.003 [a]
GGT (median(IQR)) (IU/L)	109 (37-120)	34 (17-64)	23 (13.5-33.5)	0.000 [a]
Total bilirubin (median(IQR)) (mg/dl)	1.62 (1.89-6.3)	0.58 (0.42-1.06)	0.45 (0.40-0.69)	0.000 [a]
Conjugated bilirubin (median(IQR)) (mg/dl)	0.80 (0.24-4.1)	0.33 (0.21-0.56)	0.22 (0.20-0.36)	0.000 [a]
Total IgG (median(IQR)) (mg/dl)	2285 (2129-3226)	1680 (1250-1888)	1260 (1030-1482)	0.000 [a]
Albumin (median(IQR)) (mg/dl)	4.10 (3.25-4.40)	4.30 (4.24-4.74)	-	0.002 [b]
PT (median(IQR)) (s)	15.5 (14-18.8)	13.8 (13.3-15.5)	-	0.009 [b]
INR (median(IQR))	1.3 (1.17-2.26)	1.15 (1.09-1.36)	-	0.001 [b]
Legend: IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase;				
GGT, □-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; PT, prothrombin time				
* a: Related-samples Friedman's test ; b: Wilcoxon signed ranks test.				

Table-4: Autoantibody profile in children with AIH

Autoantibody	Type-1 AIH	Type-2 AIH
ANA	9	1
SMA	11	0
LKM-1	0	3
AMA	0	2
p-ANCA	4	2
ANA+SMA	7	0
LKM-1 +AMA	0	2
Legend: ANA, antinuclear antibodies; SMA, Anti-smooth muscle antibodies;		
LKM-1, liver-kidney microsomal antibodies-1, AMA, antimitochondrial antibodies;		
p-ANCA, Perinuclear antineutrophil cytoplasmic antibodies.		

in settings of concomitant autoimmune diseases. IgG is usually raised at presentation in both types (3,7,22). as well as in the present study where independently of mode of presentation or association of other autoimmune or auto-inflammatory disease, the total IgG levels were elevated in all the patients. Yassin et al (23) reported elevated IgG levels at least 1.5 times and above in all the children with AIH. However, some pediatric studies showed IgG levels increment in only 60-85 % of the patients (6,24). Pando et al revealed that children with either acute or non-acute onset of the disease had significantly higher levels of total IgG at presentation compared to adults (21). The detection of several autoantibodies is still the hallmark of the diagnosis (1,15). Autoimmune profile of our patients was consistent with diagnosed type, however two children with type 2 AIH and positive anti- LKM 1 antibody had also AMA positivity. Although AMAs remain the serological hallmark for PBC diagnosis, in 3.6% to 34% of the patients with AIH, especially in type-2, AMA presence was reported (11, 25). Nevertheless, most researchers agree that the presence of AMA in AIH does not identify a subgroup of patients requiring different therapeutic options or leads to development of PBC (11). In addition, a long-term Canadian trial has shown that in patients with classical AIH who were AMA-positive over a follow-up of up to 27 years did not develop PBC (26).

In all patients with suspected AIH, including those with acute presentation with normal coagulation parameters, a liver biopsy should be performed, not only for diagnosis but also for the evaluation of disease severity (8,15). The present study showed that even in the acutely presented subjects liver biopsy could be safely done after normalization of the coagulation parameters.

Treatment improves the prognosis and reduces the formation of fibrosis and progression to cirrhosis in patients with AIH (9,11). Children with AIH usually well respond to immunosuppressive treatment with corticosteroids combined with immunomodulators. (15, 27). Standard maintenance therapy for all forms of AIH is the combination of low doses of prednisone and azathioprine (9,15), however in case of intolerance to AZA, MMF or cyclosporine usage is recommended (28). In the present case series Azathioprine was discontinued in two patients; in the first, because of severe skin eruptions and second child had persistent pancytopenia. In these cases, MMF was introduced. The expected frequency of remission with treatment is around 80% (6, 15, 28). This was observed also in the current case series, where complete response to treatment was achieved in 94% of the children. Only one patient had treatment failure (6%), because of non-adherence. Interestingly a study comparing pediatric and adult subjects with AIH showed that despite the higher doses of immunosuppressives in children, the treatment response was poorer compared to adults, suggesting that pediatric and adult AIH are different clinical entities with genetic associations (21). Rodriguez et al. also observed lower frequencies of treatment response (78.3%) with frequent relapses in children and adolescent with AIH (16). Teufel et al. (17) compared the rates of relapses of AIH in patients with and without CAIDs and found no significant differences in the number of relapses between the groups. However, in a multicenter study from Netherlands, CAIDs were shown to be independent risk factor for early relapse in AIH patients after withdrawal of immunosuppression (19).

Unlike in adults, the criteria for discontinuation of the treatment for children with AIH has not been clarified. Adult guidelines recommend withdrawal of therapy for patients who achieved a complete response after two years of treatment, and in absence of histological cirrhosis, yet it's not clear if remission also includes the disappearance of the autoantibodies (5,29). Pediatric hepatology committee suggests treating children for at least 2 to 3 years and withdrawal of treatment if transaminase and IgG levels have been normal with negative autoantibodies for at least one year (15). According to this protocol, successful complete withdrawal of treatment however is possible only in 20% of patients with AIH-1, but not possible in AIH-2, with relapse in 45% of the children (8,15). Here with, none of the presents study subjects fulfilled criteria for ceasing therapy.

The present trail had few limitations. First, this report includes a relatively small number of patients, accordingly a large population from multicentric date are needed in order to review the association of AIH with other autoimmune or autoinflammatory diseases in children. On the other hand, the data were retrospectively collected, so a prospective, well-structured study would give more precise results featuring AIH and CAIDs in children.

Conclusion: AIH is a rare but important cause of chronic liver disease in children. AIH must always be included in the differential diagnosis of elevated liver enzymes in children, as early treatment avoids progression to cirrhosis. Frequent association with autoimmune or autoinflammatory diseases also should be kept in mind as the clinical expression of the concomitant disease can be extremely variable therefore diagnosis and treatment delay may occur (18, 30). Accordingly pediatric hepatologist should be aware of this association and prompt follow up should be designed for children with multiple CAIDs.

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