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Pediatric autoimmune liver disease and extra-hepatic immune-mediated comorbidities

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ABSTRACT

Background: Autoimmune liver disease (AILD) includes autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC). AILD is often associated with other extra-hepatic immune-mediated disorders (EDs), but there are few pediatric studies available to date. In this study we evaluated the association between AILD and EDs in our pediatric series.
Methods: In this single centre retrospective study 48 patients (39 AIH and 9 ASC children) were evaluated. Thirty-six children were primarily referred to our Centre for liver disease suspicion, while the remaining twelve had a previous diagnosis of EDs. All the patients were screened for various EDs at AILD diagnosis and yearly during the follow-up.
Results: Mean duration of follow-up was 9 years and 1 month. Twenty-two (46%) patients had a diagnosis of EDs. Ulcerative colitis (UC) was the most frequent EDs (9 patients), followed by autoimmune thyroid disease (5 patients) and celiac disease (5 patients). In 7 out of 9 UC patients, ASC was present.
Conclusions: Our study showed a high association (46%) between AILD and EDs. In particular, in 8 out of 9 ASC patients UC was diagnosed (p-value 0.007). It is important to look for EDs in AILD children and, conversely, AILD in EDs children with abnormal liver function tests.
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1. Introduction

Autoimmune liver disease is a chronic and progressive inflammatory disorder that evolves spontaneously to cirrhosis and liver failure. It is characterized by chronic inflammation of the liver with elevated transaminase levels, presence of specific circulating autoantibodies and increased levels of immunoglobulins G (IgG). Its pathogenesis seems to be multifactorial, including genetic susceptibility, abnormal regulation of the immune response, and environmental triggers [1–4].

Autoimmune hepatitis (AIH) is classified in two subtypes according to the presence of specific serum autoantibodies: AIH type 1 with anti-smooth muscle (ASMA) and/or antinuclear autoantibodies (ANA) positivity, and AIH type 2 with anti-liver kidney microsomal (LKM-1) and/or anti-liver cytosol type 1 (LC-1) autoantibodies positivity. AIH type 1 can affect patients of all ages, while AIH type 2 is more frequent in the pediatric age. Furthermore, a seronegative form of AIH responsive to immunosuppressive therapy is also reported in several pediatric studies [5]. On histology, AIH is characterized by interface hepatitis (i.e. inflammatory mononuclear/plasma cell infiltrate of the portal tracts expanding into the liver lobule with erosion of the limiting plate); in longstanding disease process advanced fibrosis or cirrhosis can be found.

Autoimmune sclerosing cholangitis (formerly called AIH/sclerosing cholangitis overlap syndrome), similarly to AIH, presents autoimmune features (i.e. ANA ASMA, hypergammaglobulinemia, and interface hepatitis). Moreover, this condition is characterized by the presence of perinuclear anti-neutrophil cytoplasmic antibodies, and elevated levels of gamma glutamyl transpeptidase (gamma-GT), not always present at the onset of the disease. Finally, bile ducts involvement at cholangiography is shown, with possible associated intra-hepatic bile ducts damage at liver biopsy [4,5].

AILD can be frequently associated with other immune-mediated disorders. Several studies have been published in adults focusing on the association between AILD and other immune-mediated disor-

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ders [6–12]. This association ranges from 26% to 40% [6–8]; the most frequent reported associated diseases are autoimmune thyroid disorders followed by Sjogren's syndrome [13]. There are only few pediatric case series, large pediatric cohorts are still lacking [14,15]. Extra-hepatic involvement in autoimmune liver disease is related to interactions between genetic susceptibility, environment, and immune system; this immune-mediated association could be a part of multiple organ involvement in a single systemic autoimmune disease, or, conversely, a common pathogenetic pathway could link different immune-mediated disorders [13,16].

In the recent ESPGHAN position paper on the diagnosis and management of pediatric AILD, a family history of autoimmune disease and an association between AILD and other immune-mediated disorders (EDs) are frequently reported [17]. Extra-hepatic immune-mediated disorders can precede, be concomitant, or follow liver involvement [17].

In this study we aimed to evaluate the association between autoimmune liver disease and EDs in our pediatric series and to assess the possible differences between AILD children with or without EDs.

2. Methods

A retrospective analysis of 48 pediatric clinical records (39 AIH and 9 ASC children, 24 females) was carried out in search for a concurrent diagnosis of EDs. All the patients were referred to the Pediatric Liver service of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan during the last 25 years. Thirty-six children were initially followed for abnormal liver function tests and AILD was diagnosed. The remaining twelve patients, with a previous diagnosis of other immune-mediated EDs, were referred to our Centre by other tertiary care services when abnormal liver function tests were noticed.

AIH diagnosis was made on the basis of the International AIH group score [18,19]. ASC diagnosis was based on specific biochemical features (i.e. autoantibodies positivity, hypergammaglobulinemia, elevated levels of GGT, etc.) and presence of bile ducts involvement at cholangiography and liver biopsy [18,20]. Other causes of chronic liver disease, such as viral, metabolic, and genetic disorders were ruled out as a cause of hepatic involvement.

A complete diagnostic tool of exams was performed to early diagnose any EDs (see Table 1): all the patients were screened at AILD diagnosis and every year during the follow-up for inflammatory bowel disease, celiac disease, and other immune mediated disorders such as, autoimmune thyroiditis, autoimmune skin disease, rheumatoid arthritis, diabetes, and lupus erythematosus.

Table 1
Diagnostic serological and instrumental exams used for EDs diagnosis.

Serological or instrumental exams	
Complement tests (C3, C4), anti-dsDNA, Ig classes and subclasses, anti-centromere antibody, anti-Scl-70 antibodies	Immunological, reumathological disease (lupus, scleroderma)
Anti-tGAse Abs, Total IgA, HLA A-B-C DRB DQ2-8	Celiac disease
Abdominal bowel ultrasound	Crohn's disease, inflammatory bowel disease
Faecal calprotectin, faecal blood occult test, ANCA (p-ANCA, c-ANCA)	
FT3, FT4, TSH; thyroid Abs profile (TPO/TG)	Autoimmune thyroid disease

Abbreviations: anti-dsDNA, anti-double stranded DNA antibody; HLA, human leukocyte antigen; tGAse, transglutaminase; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TPO, thyroid peroxidase antibodies; TG, thyroglobulin antibodies.

Furthermore, in the two subgroups of children with (group A) or without (group B) EDs, we evaluated:

a) family history for autoimmune disorders,
b) liver function tests at AILD diagnosis,
c) demographic features,
d) AILD characteristics and severity including stable long-term remission free of therapy (>5 years).

All patients underwent standard immunosuppressive therapy with steroids plus azathioprine, while cyclosporine was used only when steroid therapy was considered contraindicated (i.e. reduced bone density, severe gastritis at upper gastrointestinal endoscopy).

Furthermore, ursodeoxycholic acid therapy was added to immunosuppressive therapy in ASC patients.

2.1. Statistical analysis

Statistical analysis was performed using Stata 15.0 (Stata Corporation, College Station, TX, USA). A descriptive analysis of the cohort was performed for the patients' baseline characteristics. Categorical data were presented as absolute numbers and percentages, while quantitative data as median and interquartile range. Proportions were compared using Fisher's exact test. Comparisons between groups were obtained from the direct comparison of medians (median regression of outcome variable vs. predictor). A p-value less than 0.05 was considered significant.

3. Results

In our pediatric series 28 patients (58%) had a diagnosis of AIH type 1 (14 females), 10 patients (21%) a diagnosis of AIH type 2 (6 females). One female patient had a diagnosis of seronegative AIH. The remaining 9 patients (19%) presented autoimmune sclerosing cholangitis (3 females).

Mean age at AILD diagnosis was 10 years and 2 months.

All patients were negative for other chronic liver disease. Abnormal liver function tests (notably transaminases) and elevated levels of IgG were present in all the children at AILD diagnosis. High titres of specific autoantibodies were present in all the patients but one. In particular, 8 out of 9 ASC patients showed p-ANCA autoantibodies positivity. Children with a diagnosis of autoimmune sclerosing cholangitis had also high gamma-GT levels.

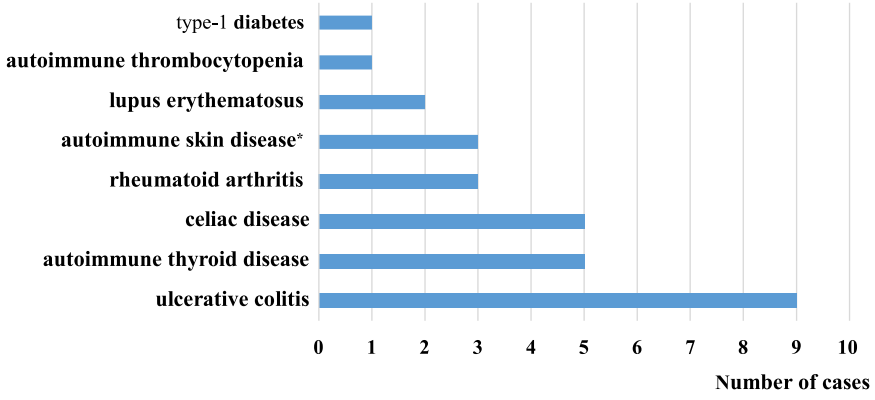
Conventional IS therapy (prednisone 2 mg/kg, slowly tapered to the lowest dose to control the disease, plus azathioprine 1–2 mg/kg) was used in the majority of patients; cyclosporine was administered in three patients with serious contraindications to steroid treatment (i.e. reduced bone density, severe gastritis at upper gastrointestinal endoscopy). In the 9 ASC patients ursodeoxycholic acid therapy was added to immunosuppressive therapy.

At liver disease onset 22 (46%) patients were clinically asymptomatic, 14 (29%) showed non-specific symptoms (fatigue, anorexia, and abdominal pain), 6 (12%) signs of acute hepatitis, 5 (10%) pre-existing symptoms of inflammatory bowel disease, 1 (2%) acute liver failure.

Furthermore, among the 9 AILD patients with associated ulcerative colitis, intestinal symptoms preceded liver function tests abnormality in 5 patients, while intestinal and hepatic symptoms were concomitant in 2 of them; the remaining 2 children had liver disease as the first manifestation.

Mean duration follow-up was 9 years and 1 month (range 10 months–20 years 7 months).

In our series a strong association between EDs and AILD (46%–22/48 patients) was noticed. In particular, 7 out of 22 (32%) children presented more than one immune mediated extra-hepatic



*2 patients with scleroderma and 1 patient with psoriasis

Fig. 1. Immune-mediated extra-hepatic disorders in AILD children.

Table 2
Characteristics of AILD patients with more than one associated immune-mediated EDs.

Patient, gender, type disease	EDs
1, M, ASC	IBD, thyroiditis
2, M, ASC	IBD, arthritis
3, F, ASC	IBD, thyroiditis
4, F, AIH type 1	Diabetes, celiac disease
5, F, AIH type 1	Arthritis, scleroderma
6, F, AIH type 1	Thyroiditis, celiac disease
7, M, AIH type 1	Lupus erythematosus, psoriasis

Abbreviations: M, male; F, female; ASC, autoimmune sclerosing cholangitis; EDs, extra-hepatic immune-mediated disorders; AIH, autoimmune hepatitis; IBD, inflammatory bowel disease.

disorder (Table 2). In this subgroup, a higher prevalence of female gender and AIH type 1 was found. Ulcerative colitis was the most frequent associated disease (19%; 9/48). Other associated immune mediated disorders were: autoimmune thyroid diseases (10%; 5/48), celiac disease (10%; 5/48), autoimmune skin disease – scleroderma and psoriasis – (6%; 3/48), rheumatoid arthritis (6%; 3/48), lupus erythematosus (4%; 2/48), autoimmune thrombocytopenia (2%; 1/48) and type-1 diabetes (2%; 1/48) (Fig. 1). Interestingly, in 8 out of 9 ASC children a strong statistically significant association with EDs was found (p-value 0.007); in particular, 7 presented ulcerative colitis and 1 lupus erythematosus. The remaining two children with UC had a diagnosis of AIH type 1.

Fifteen (68%) out of twenty-two children presented EDs before or concomitant to AILD diagnosis, while in the remaining seven, EDs were subsequent to AILD (Fig. 2). The statistical analysis of the three groups of patients with AIH type 1, AIH type 2 and ASC showed no statistical difference regarding the onset of EDs.

In particular, family history for autoimmune disease was comparable in AILD children with (group A) or without EDs (group B), 27% vs. 35%, (p-value = 0.756).

In group A the median value of transaminases and gamma GT at AILD diagnosis was comparable to group B (Table 3). Moreover, the median value of transaminases and gamma-GT levels at AILD diagnosis in the two subgroups of EDs children (before or concomitant AILD diagnosis vs. EDs after AILD diagnosis) was also comparable. Although not statistically significant, the subgroup of children with EDs after AILD diagnosis was younger than the other subgroup (9 years and 3 months vs. 11 years and 6 months, p-value 0.46).

On histology, cirrhosis at first biopsy of AILD diagnosis was more frequent in the group B compared to group A (28% vs. 14%, p-value 0.30).

Disease progression in terms of number of AILD relapses was higher in the group A than in the group B. Finally, only 2 out of 22 children (9%) in group A showed a stable long-term remission (free of therapy and relapses) compared to 5 out of 26 (19%) in the group B.

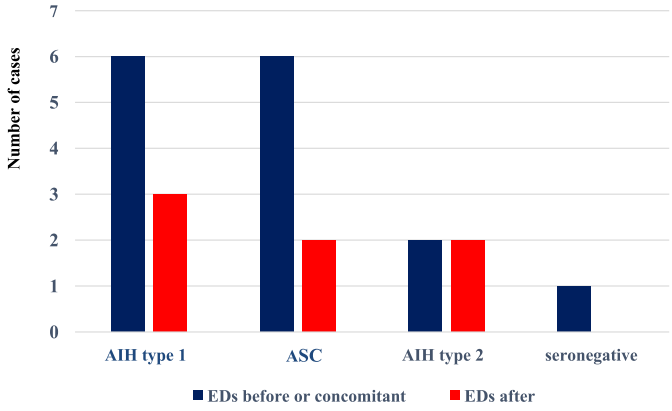


Fig. 2. Comparison between patients with EDs before or concomitant to liver involvement and patients with EDs after AILD diagnosis.
Abbreviations: ASC: autoimmune sclerosing cholangitis; AIH: autoimmune hepatitis; EDs: extra-hepatic immune mediated disorders.

Table 3
Comparison of demographical and biochemical parameters at diagnosis in AILD children with or without EDs.

	EDs+ (n = 22)	EDs− (n = 26)	p-Value
Gender, male[a]	11 (50)	13 (50)	1.0
Age at diagnosis (years)[b]	10.5 (6.4–13.4)	10.2 (6.5–12.2)	0.84
AST (U/l)[b]	340 (132–503)	327 (173–1291)	0.94
ALT (U/l)[b]	349 (208–549)	491 (216–1268)	0.41
GGT (U/l)[b]	82 (41–345)	74 (20–158)	0.81
IgG levels (IU/ml)[b]	1.9 (1.6–3.3)	1.9 (1.6–3.1)	0.74
Seronegative AIH[a]	1 (4.5)	0 (0)	0.46
AIH type 1[a] (n = 28)	9 (40.9)	19 (73.1)	**0.039**
ASC[a] (n = 9)	8 (36.4)	1 (3.8)	**0.007**
ANA	15/17	14/20	0.25
ASMA	12/17	17/20	0.43
AIH type 2[a] (n = 10)	4 (18.2)	6 (23.1)	0.74
LKM1	4/4	5/6	1.0
LC1	1/4	3/6	0.57

Abbreviations: AILD, autoimmune liver disease; EDs, extra-hepatic immune-mediated disorders; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase; IgG, immunoglobulin G; AIH, autoimmune hepatitis; ASC, autoimmune sclerosing cholangitis; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibody; LKM1, liver kidney microsome antibodies type 1; LC1, Antibody to liver cytosol.

[a] Number (percentage) — Fisher'exact test.

[b] Median (1st–3rd quartile) — median regression of outcome variable vs. predictor.

Table 4
Immune-mediated extra-hepatic involvement in adults and children.

Adult studies	
Author, year, reference	Association between EDs in AILD
Muratori et al., 2015 [6]	101/327 AIH (29.9%)
Teufel et al., 2010 [7]	111/278 AIH (40%)
van Gerven et al., 2014 [8]	335/1313 AIH (26%)
Pediatric studies	
Author, year, reference	Association between EDs in AILD
Gregorio et al., 1997 [4]	11/52 AIH (21%)
Vajro et al., 2013 [14] — meta-analysis	Pooled prevalences of CD in AIH 6.3%
Nastasio et al., 2013 [15]	15/79 AIH (19%)[a]

Abbreviations: EDs, extra-hepatic disorders; AILD, autoimmune liver disease; AIH, autoimmune hepatitis; CD, celiac disease.

[a] This percentage is related only to 15 children with celiac disease.

4. Discussion

Autoimmune liver disease can be frequently associated with other immune mediated extra-hepatic disorders, despite the published reports are few. Moreover, the exact pathophysiological mechanism underlying this condition is still unknown. The published reports are summarized in Table 4.

Our study showed a high association between AILD and other immune-mediated EDs in children, as we found a 46% rate of associated immune mediated disease in our AILD pediatric series.

Our results are consistent with previous adults' studies: Teufel et al. in their cohort study showed that 111 (40%) of 278 patients with AIH had a diagnosis of additional autoimmune disease [7]. Muratori et al. study found at least one extra-hepatic autoimmune disease in 101 of 327 (29.9%) adult patients with a diagnosis of AIH [6]. A larger adult study found concomitant autoimmune disease in 335 out of 1313 AIH patients (26%) [8]. To our knowledge there are no reported data about large pediatric series but only case-reports.

Based on these findings, it is important to always search for AILD in a child with other extra-hepatic immune mediated diseases when abnormal liver function tests are noticed and vice-versa.

In our study, the well-known strong association between ulcerative colitis and autoimmune sclerosing cholangitis was confirmed (p-value 0.007), as previously reported [7,10–13,21,22].

Several studies highlighted a frequent association between AILD and autoimmune thyroid diseases. We found in our study a 10% of patients with autoimmune thyroiditis, comparable with the percentage between 8% and 15% reported in adult studies [6,7,23]. Biró et al. assumed that the high prevalence of autoimmune thyroid diseases in patients with other immune-mediated disorders could be explained by HLA-dependent genetic factors, cross-reactivity of anti-thyroid autoantibodies with other tissue antigens and auto-reactive T cells or shared epithelial antigens as potential pathophysiological mechanisms [9]. Furthermore, an interesting review article reported that celiac disease and autoimmune hepatitis could be genetically linked because both disorders express selected combinations of genes coding for class II HLA molecules on chromosome 6 [24]. For this reason, it is important to screen for concomitant liver involvement every patient with a diagnosis of immune mediated EDs, performing liver function tests and specific autoantibodies, especially in children with ulcerative colitis, autoimmune thyroid diseases and celiac disease.

Our results showed no statistical difference in children with or without EDs in terms of clinical characteristics and hepatic involvement, as already reported in adults [6,7]. Furthermore, we could not find a statistical difference in terms of frequency in the association between EDs and AIH type 1 or type 2, even though the small number of AIH type 2 patients could be a limiting factor (see Table 3).

The lower percentage of children with severe histological involvement in group A could be related to the frequent blood exams performed for the pre-existing EDs, that lead to an earlier diagnosis of liver disease compared to group B.

A previous Dutch study showed that AIH patients with other autoimmune diseases had an independent risk factor for early relapse after withdrawal of immunosuppression [25]. This apparently worse prognosis in EDs patients would seem confirmed by our results, with a lower percentage of long-term remission of AILD disease in this group of children. Further large pediatric studies are needed to validate these findings.

Recently, Guo et al. [13] reviewed studies published in adult population on the association between extra-hepatic autoimmune diseases and AILDs showing an incidence of extra hepatic involvement in AILDs patients between 30% and 61,8%; results that are comparable to those found in our pediatric series.

They also stated the necessity of an accurate evaluation for EDs in AILD patients to ensure an early detection and a better outcome [13].

Our study is not exempt from some limitations. Firstly, this is a retrospective study conducted in a third-level pediatric hospital centre, which possibly could overestimate the percentage of some EDs because children are referred by other third-level centers.

Furthermore, there are other rare immune-mediated disorders (i.e. autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, Behçet disease, Sjogren syndrome, glomerulonephritis, etc.) not mentioned because not present in our patients.

In conclusion, our study confirms the strict association between autoimmune liver disease and other immune mediated disorders also in the pediatric age.

Conflict of interest
None declared.

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