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Autoimmune hepatitis and immune dysregulation: A case series

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ABSTRACT

Objective: To assess the presence of inborn errors of immunity (IEI) in a pediatric autoimmune hepatitis (AIH) cohort.
Study design: This retrospective study included patients aged 0-18 diagnosed with AIH in our center between 1995 and 2023 and followed by the immunology department for a clinical and/or molecular IEI diagnosis.
Results: Among our 83 AIH patients, five (6%) displayed signs of associated IEI. Two of those patients had a genetic confirmation of IEI (SP110 and AIRE homozygous mutations). IEI-related signs were recurrent infections (n=3), immune-mediated cytopenia (n=4) or skin disease (n=2) and autoimmune polyendocrinopathy (n=1). The four patients diagnosed with seronegative AIH responded to immunosuppressive therapy, while the AIH type 2 patient underwent emergent liver transplantation for fulminant liver failure at diagnosis.
Conclusion: Our small case series highlights the need to look for signs of immune dysregulation in AIH patients. Conversely, as AIH can be atypical in IEI, the threshold should be low to perform a diagnostic liver biopsy in IEI patients suffering from chronic cytolysis. We believe that systematic genetic testing and immune phenotyping of AIH patients who display signs of immune dysregulation will be crucial to better understand the close link between AIH and IEI.
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1. Introduction

Autoimmune hepatitis (AIH) is an infrequent immune-mediated inflammatory disease of the liver, leading to cirrhosis and liver dysfunction in the absence of effective therapy. Regulatory T-cell dysfunction plays a central role in AIH physiopathology and leads to loss of tolerance towards self-liver antigens, resulting in CD4 and CD8 T-cell activation [1]. The induced pro-inflammatory cascade leads to immune activation of macrophages, natural killer cells and B-cells, and the production of autoantibodies.

Autoimmunity is a classical feature of inborn errors of immunity (IEI) and is usually associated at various degrees with infection susceptibility, atopy and/or increased risk of malignancy. It reportedly occurs as a first disease manifestation in 18 % of patients with IEIs and is the only manifestation in approximately 10 % of cases [2]. Unlike autoimmune disorders encountered in the general population that mostly present in female adults and confine to one tissue, autoimmunity in IEIs displays an early onset, has no evident sex preference, and is frequently multisystemic [3].

The liver is a common site of autoimmunity in IEI, further expanding the morbidity and mortality in this population [4,5]. Hepatic injury can present through a wide variety of hepatobiliary diseases in IEI patients, including nodular regenerative hyperplasia, granulomatous hepatitis, non-cirrhotic portal hypertension, hepatic veno-occlusive disease, cryptosporidium-related sclerosing cholangitis, infectious hepatitis and AIH [4]. AIH has been described in some patients when studying IEI cohorts, and a few case reports about AIH and IEI have been published (Table 1). However, no study specifically looked for IEI/immune dysregulation in a cohort of AIH patients to date. We describe five pediatric AIH patients who were diagnosed with IEI before, during or after AIH diagnosis. Our data emphasizes the need not only to screen IEI patients for hepatic disease, but also to look for IEI/immune dysregulation in AIH patients actively.

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Table 1
Non-exhaustive overview of existing literature about autoimmune hepatitis in patients suffering from inborn errors of immunity.

Inborn error of immunity	Reference	Number of patients	AIH subtype	Age at AIH diagnosis (years)	Sex
Primary immunodeficiencies					
Partial ADA deficiency	Somech 2009 [6]	1	Type 2	1	M
CVID	Lorenzini 2020 [7]	3	NA	NA	NA
	Fuss 2013 [8]	4	Seronegative	8–47	3M/1F
	Myneedu 2021 [9]	1	Seronegative	27	F
	Pollock 2020 [10]	1	Type 1	44	F
	Queiros 2018 [11]	1	Seronegative	28	F
	Cakir 2023 [12]	1	Type 1	3	F
	Klemann 2019 [13]	1	Type 1	17	F
Primary immune regulatory disorders					
IPEX syndrome	Gambineri 2008 [14]	1	NA	Neonatal	M
	Lopez 2011 [15]	1	Type 2	4	M
APECED	Zaidi 2017 [16]	2	Type 2	2–5	NA
	Perheentupa 2006 [17]	4	NA	< 16	NA
	Meloni 2012 [18]	6	NA	≤ 12	5F/1M
	Chascsa 2021 [19]	18	NA	2–31	13F/5M
STAT1 GOF disease	Toubiana 2016 [20]	6	NA	< 18	2F/4M
	Hori 2012 [21]	1	Type 2	22	F
	Hadzic 2024 [22]	1	Type 2	1	F
STAT3 GOF disease	Fabre 2019 [23]	4	Type 1	NA	NA
ALPS	Pensati 1997 [24]	1	Type 2	4	F
Auto-inflammatory disorders					
Haploinsufficiency A20	Pandurangi 2023 [25]	4	3 Type 2/1 seronegative	1–13	2F/2M
	Hegarty 2024 [26]	1	Seronegative	3	M

ADA: adenosine deaminase; ALPS: autoimmune lymphoproliferative syndrome; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CVID: common variable immune deficiency; GOF: gain of function; IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked; NA: not available; STAT: signal transducer and activator of transcription.

2. Methods

The medical charts of patients aged 0–18 diagnosed with AIH and followed at the pediatric hepatology unit of our center between 1995 and 2023 were retrospectively reviewed ($n = 83$). Six of those 83 patients were concurrently followed by the immunology department for a clinical and/or molecular diagnosis of IEI. Among those six patients, five were genetically tested with an immunodeficiency panel and included in the study, regardless of the timing of IEI diagnosis/suspicion (before, during or after AIH diagnosis). The last patient was excluded due to the absence of clinical/genetic confirmation of the suspected IEI. No AIH patient was genetically tested for IEI without being followed by the immunology department. The genetic immunodeficiency panel of our patients was performed by Blueprint Genetics® (Marlborough, MA, USA) as part of the Primary Immunodeficiency panel plus (383 genes) (https://blueprintgenetics.com/tests/panels/immunology/primary-immunodeficiency-pid-and-primary-ciliary-dyskinesia-pcd-panel/). Given the association between AIH and IEI, treatment decisions were made on a case-by-case basis rather than following the standard regimen of prednisone and azathioprine [1]. The reasons that conducted our treatment choices are detailed in the Clinical Cases section, and debated in the Discussion. When rituximab was used, it was prescribed according to one of the two following described treatment regimens: systematic administration 1x/6 months, or induction treatment with four weekly doses and then further administrations according to the follow-up of B-cell depletion [27]. This project was approved by the Institution Centre Hospitalier Universitaire Sainte-Justine (Montreal, CA). A waiver of consent was obtained in accordance with the institutional policy due to the retrospective nature of this case series.

3. Clinical cases

Among the 83 patients who were followed in our center for confirmed AIH, five patients (6 %) displayed additional signs of immune dysregulation, for which they were concurrently followed by the pediatric immunology unit, and were genetically tested with an immunodeficiency panel. Those five patients' baseline characteristics and the evolution of their immune and liver disease under treatment are summarized in Tables 2–5. Representative images of the patients' liver histology are shown in Fig. 1.

Patient 1 was diagnosed with a homozygous mutation of *SP110* (Table 2) at 5 years old in the context of hypogammaglobulinemia associated with repeated severe pneumonia and bronchiectasis, which led to a sequential resection of the right lung. Five years later, he underwent a liver biopsy for repeated abnormal liver tests and was diagnosed with AIH. He was subsequently reclassified as autoimmune sclerosing cholangitis (ASC) due to anomalies of his intra- and extra-hepatic biliary tract that were evidenced on a cholangio-MRI in addition to his AIH diagnosis. He initially completely normalized his liver tests in response to treatment, including 4 doses of rituximab as an induction medication and long-term azathioprine for maintenance therapy. A B-cell-targeted induction strategy was preferred to the use of prednisone due to the need to control autoimmune liver inflammation, while minimizing the risk of immunosuppression-related complications in a patient with recurrent severe infections and structural lung damage. During follow-up (FU), he displayed recurrent mild elevation of transaminases (maximum 2x upper limit of normal - ULN) and GGT (maximum 3xULN). However, his FU biopsy showed complete resolution of liver inflammation and improvement of both fibrosis and biliary damage 5 years after ASC diagnosis. The liver function remained normal. A bone marrow transplant was discussed for this patient at the time of the lung resection, but was not performed due to his favorable respiratory evolution following immunoglobulins (Ig) replacement. Of note, homozygous *SP110* mutations classically lead to veno-occlusive disease with immunodeficiency syndrome (VODI). Still, our patient did not display any signs of veino-occlusive disease during his FU, and his immune phenotype was thereby classified as common variable immunodeficiency (CVID).

Table 2
General and immune deficiency/dysregulation characteristics of the cohort.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	M	F	F	M	F
Age at ID diagnosis	5 years	6 years	6 years	3 years	3 years
Family history of auto-/dys-immunity	None	None	None	Yes	None
Parental consanguinity	Yes	Yes	No	No	No
Associated conditions	Neutropenia, failure to thrive, recurrent pneumonia	Autoimmune hemolytic anemia, immune thrombopenia, recurrent pneumonia	Autoimmune neutropenia, atopic dermatitis, recurrent infections	Adrenocortical insufficiency, hypoparathyroidism, functional asplenia, growth hormone deficiency, hypothyroidism (APECED type 1)	Autoimmune hemolytic anemia, atopic dermatitis
Ethnicity	Lebanese	Innu	Caucasian	Caucasian	Beninese/ Caucasian
Genetics	Homozygous mutation of *SP110* (NM_080424.4: c.642del)	Heterozygous VUS in *LYST* (c.8312C>*T*), *IL10RA* (NM_001558.4: c.1002G>*C*) and *CECR1* (c.1135A>*T*)	Heterozygous VUS in *STAT1* (c.1582+3A>*G*) and *IL17RA* (c.551–2A>*G*)	Homozygous mutation of *AIRE* (exact mutation not available)	Heterozygous VUS in *NOD2* (NM_001293557.2: c.549G>*T*) and *CARD11* (NM_032415.7: c.2735G>*A*)
Immune phenotype	CVID	CVID	PIRD	Immune dysregulation	PIRD

AIH: autoimmune hepatitis; APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CVID: common variable immunodeficiency; Ig: immunoblobulins; PIRD: primary immune regulatory disorder; VUS: variant of unknown significance.

Table 3
Immunological features of the cohort at the first assessment in our center.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at evaluation	5 years	6 years	6 years	10 years	12 months
Total lymphocyte count, μL	2400	13,930	3000	4600	9100
$CD3^+$ (/μL)	2064 (1634–3182)	**8776** (1371–2554)	2460 (1371–2554)	**3910** (1344–2110)	**6461** (2832–4805)
$CD3^+CD4^+$ (/μL)	1248 (899–2038)	**4597** (735–1549)	1410 (735–1549)	**1610** (694–1317)	**4914** (1823–3365)
$CD45RA^+CD31^+/CD4^+$ (%)	52 (48–68)	64 (47–65)	52 (47–65)	45 (35–60)	68 (59–73)
$CD3^+CD8^+$(/μL)	864 (459–1001)	**4458** (378–832)	780 (378–832)	**2162** (366–642)	**2184** (645–1420)
CCR7+CD45RA+/CD8+ (%)	NA	NA	57 (46–89)	NA	NA
CCR7+CD45RA-/CD8+ (%)	NA	NA	1 (0–13)	NA	NA
CCR7-CD45RA-/CD8+ (%)	NA	NA	10 (0–28)	NA	NA
CCR7-CD45RA+/CD8+ (%)	NA	NA	32 (8–41)	NA	NA
HLA-DR/CD3+ (%)	NA	NA	NA	NA	3 (N < 10)
$CD19^+$ (/μL)	**144** (363–820)	**4458** (266–589)	411 (266–589)	345 (226–500)	1638 (751–1865)
$CD27^+/CD19^+$ (%)	**0.03** (N > 8)	**0.01** (N > 8)	0.19 (N > 8)	0.56 (N > 8)	0.12 (N > 8)
$CD3^-CD56^+$ (/μL)	118 (95–455)	**390** (131–333)	138 (131–333)	156 (102–361)	264 (197–934)
CD4-CD8-TCRab /CD3_ (%)	NA	NA	2.3	1.7	NA
FasL (pg/mL)	NA	NA	440 (N < 360)	<200	NA
IgG (g/L)	8.37 (5.4–13.6)	6.89 (5.4–13.6)	**14.53** (5.4–13.6)	**17.6** (5.4–13.6)	**18.79** (3.2–11.5)
IgA (g/L)	0.18 (0,30 - 1,50)	0.76 (0,50 - 2,20)	**2.53** (0,50 - 2,20)	1.52 (0,50 - 2,20)	**1.66** (0,20 - 1,20)
IgM (g/L)	**1.63** (0,40 - 1,50)	1.05 (0,40 - 1,50)	**1.62** (0,40 - 1,50)	0.64 (0,40 - 1,50)	0.81 (0,40 - 1,50)
IgE (kU/L)	NA	NA	NA	10 (<696)	NA
Anti-diphtheria IgG (UI/mL)	< **0.01** (>0.10)	**0.01** (>0.10)	**0.08** (>0.10)	NA	0.46 (>0.10)
Anti-tetanus IgG (UI/mL)	< **0.01** (>0.10)	**0.02** (>0.10)	0.23 (>0.10)	NA	0.84 (>0.10)
Anti-measles (AU/mL)	**0.00** (>3)	**0.71** (>3)	NA	NA	**1.79** (>3)
C3 (g/L)	NA	1.16 (0.8–1.6)	NA	NA	**0.31** (0.8–1.6)
C4 (g/L)	NA	0.2 (0.2–0.5)	NA	NA	**0.04** (0.2–0.5)

NA: not available. Norms in brackets.

Table 4
Hepatic disease characteristics at diagnosis.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at AIH-like diagnosis	10 years	6 years	6 years	10 years	12 months
IEI-AIH diagnosis timing	IEI before AIH	Concomitant	Concomitant	IEI before AIH	IEI after AIH
Immuno-modulatory treatment preceding AIH diagnosis	Ig replacement G-CSF	Ig replacement	None	Hydrocortisone	None
IAIHG simplified scoring system (probable AIH ≥6) [30]	4	3	5	5	7
Juvenile AIH/ ASC score (probable AIH ≥7) [31]	6	6	6	7	7
AIH type	Seronegative → ASC	Seronegative	Seronegative	Seronegative	Type 2
ALT (U/L) (<25)	65	397	464	80	3506
AST (U/L) (<43)	78	360	225	71	5255
GGT (U/L) (<43)	108	55	82	16	131
Total (direct) bilirubin (µmol/l)	11 (2)	815 (416)	7.4 (3.5)	10 (3)	260 (179)
INR	1.00	0.96	1.07	1.04	2.99
IgG (g/L)	8.37 (5.4–13.6)	6.89 (5.4–13.6)	14.53 (5.4–13.6)	17.6 (5.4–13.6)	18.79 (3.2–11.5)
ANA	(-)	(-)	(-)	(-)	(-)
ASMA	(-)	(-)	(-)	(-)	(-)
LKM	ND	(-)	(-)	(-)	1/640
LC-1	ND	(-)	(-)	(-)	(-)
SLA	ND	ND	(-)	ND	(-)
ANCA	(-)	(-)	ND	ND	(-)
Interface hepatitis	Yes	Yes	Yes	Yes	Yes
Inflammatory infiltrate	T-cells ++ No mature B-cells, few CD79A+ Few eosinophils and monocytes	Mixed T- and plasmocytes Few eosinophils	B-cells ++, rare plasmocytes	++ Plasmocytes	T-cells +++, few neutrophils (75 % parenchymal necrosis)
Biliary impairment	Mild inflammatory infiltrate of bile ducts, ductular proliferation	Mild ductular proliferation and cholestasis	Focal biliary inflammation	Focal biliary inflammation	Moderate ductular proliferation, no biliary destruction
Fibrosis (METAVIR)	F4	F2–3	F2	F2	F2

ANA: anti-nuclear antibody; ANCA: antineutrophilic cytoplasmic antibody; ASC: autoimmune sclerosing cholangitis; ASMA: anti-smooth muscle antibody; IEI: inborn error of immunity; LC-1: liver cytosol type-1 antibody; LKM: liver-kidney microsomal antibody; ND: not done; SLA: anti-soluble liver antigen antibody. Norms in brackets.

Table 5
Evolution of liver disease.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Liver disease treatment	Rituximab Azathio-prine	Prednisone Azathio-prine MMF	Rituximab Prednisone	MMF	Liver transplant
Initial response to treatment	Yes	Yes	Yes	Yes	N/A
FU duration after AIH diagnosis	7 years	10 years	2 years	7 years	6 years
Biochemical response to treatment at last FU	Incomplete	Complete	Complete	Complete	N/A
Adherence issues	Yes	Yes	No	No	No
Positivity of auto-antibodies during FU for initial seronegative cases	Yes (ANA 1/20)	No	No	No	N/A
Timing between AIH diagnosis and last FU biopsy	5 years	10 years	1 year	N/A	2 years
Last FU biopsy features	Improved fibrosis (F3), no inflamma-tion, no ductular prolifera-tion	Stable fibrosis (F2-F3), no inflamma-tion	Comparable except for the T-cells predomi-nance in the portal infiltrate	N/A	Steatosis, very mild focal portal inflamma-tion (indetermi-nate rejection), F0

ANA: anti-nuclear antibody; FU: follow-up; MMF: mycophenolate mofetil; N/A: not applicable.

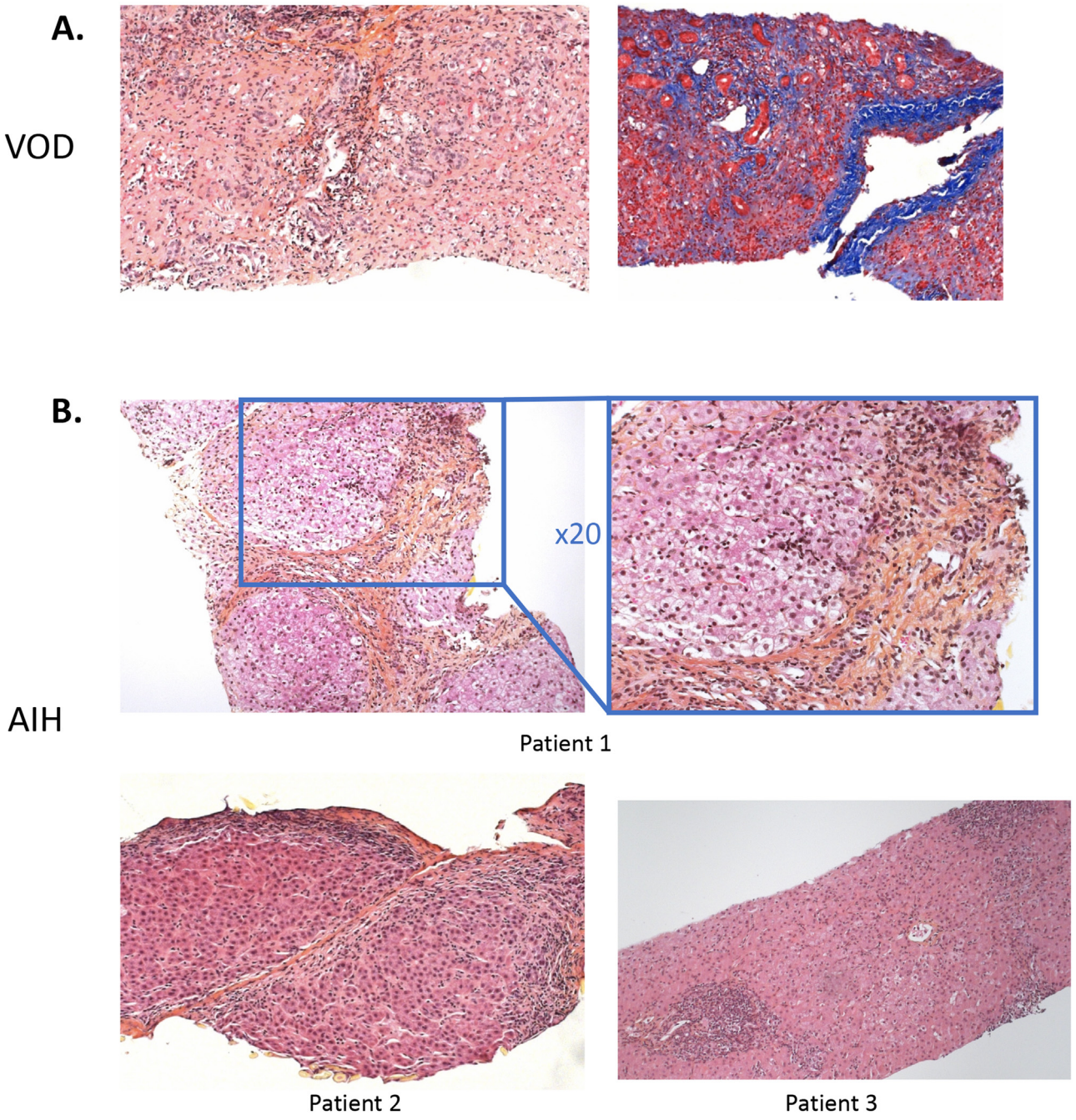

Fig. 1. Liver histology. (A) Images of hepatic veno-occlusive disease in patient 2: collapse of hepatic lobules (left image, H&E staining) with peri–sinusoidal and hepatic veins fibrosis (right image, Masson's trichrome staining); (B) Images of liver biopsies at the time of AIH diagnosis: presence in all patient of predominantly portal inflammation with interface hepatitis, various degrees of lobular inflammation and fibro-inflammatory porto-portal bridging. AIH: autoimmune hepatitis; VOD: veno-occlusive disease.

Patient 2 has a CVID diagnosis without any validated pathological mutation identified by the immunodeficiency genetic panel, nor with a full sequencing of *SP110*. She first presented at the age of five with cholestatic hepatitis and hemolytic anemia following an infectious episode. A complete work-up, including liver biopsy, liver angio-CT and invasive cavography, revealed a veino-occlusive disease that resolved spontaneously. Of note, at that time, she already had a history of hypogammaglobulinemia and immune thrombopenia that had been treated with Ig replacement in another center. One year later, she presented again with cholestatic hepatitis, and the liver biopsy was compatible with AIH. At that time, the patient displayed normal IgG levels, which was unusual for her in the context of her chronic hypogammaglobulinemia. Her immune condition was further investigated as she also suffered from repeated pneumonia, and she was started on prednisone and azathioprine along with the reintroduction of Ig replacement. Her biochemical liver tests improved following prednisone introduction, but she remained cortico-dependent and displayed repeated relapses. Mycophenolate mofetil (MMF) was then introduced as a second-line therapy, instead of azathioprine. Ten years after the diagnosis, she is now in biochemical remission under MMF monotherapy and liver histology showed a complete resolution of the inflammation. She was recently investigated for suspicion of inflammatory bowel disease in the context of diarrhea with elevated fecal calprotectin (>2000 µg/g). A gastro-duodenoscopy and a colonoscopy were carried out; histological results were compat-

ible with MMF-induced colic inflammation. The dose of MMF was slightly reduced, which allowed the resolution of diarrhea without observing any increase of liver enzymes. Of note, treatment adherence was a recurrent issue and added considerable challenge to the therapeutic management of this patient.

Patient 3 was diagnosed with AIH at the age of six. Autoantibodies were negative, but she displayed hypergammaglobulinemia, and liver histology was in favor of the diagnosis. The patient was concurrently investigated for immune deficiency as she suffered from frequent infections even before the start of immunosuppressive therapy, associated with severe atopic dermatitis and neutropenia. Two bone marrow biopsies confirmed the peripheral origin of neutropenia, therefore leading to the diagnosis of autoimmune neutropenia. She was treated with rituximab administered every 6 months as the inflammatory portal infiltrate was predominantly CD20-positive, with the aim of managing both AIH and the antibodies-mediated neutropenia. Initial response was good as the neutrophil count and liver enzymes normalized. Neutropenia did not recur, but the AIH relapsed one year later – before the third dose of rituximab –, which justified the temporary introduction of prednisone and the administration of rituximab every 4 months. Two and a half years after the diagnosis, she is now in complete biochemical remission and receives rituximab every 6 months in monotherapy. She developed secondary persistent hypogammaglobulinemia 15 months after the initiation of rituximab therapy, and required long-term Ig replacement. Her genetic immunodeficiency panel did not show any validated pathological mutations.

Patient 4 was diagnosed with APECED type 1 following his older brother's diagnosis, as they carried the same homozygous *AIRE* mutation. The patient suffered from adrenocortical insufficiency, hypoparathyroidism, functional asplenia, growth hormone deficiency and hypothyroidism. He was diagnosed with AIH at the age of ten, in the context of cytolysis associated with hypergammaglobulinemia and typical liver histology. He was started on MMF monotherapy as the disease severity was mild, and completely normalized his liver enzymes and gammaglobulins without needing prednisone as an induction therapy. He only relapsed once during his FU and did not undergo any additional biopsy due to his favorable evolution.

Patient 5 underwent an emergency liver transplantation for fulminant hepatitis secondary to type 2 AIH at the age of 1 year. Despite the acute clinical context and important parenchymal necrosis on liver histology, significant portal fibrosis on liver biopsy favored a chronic insult. Her post-transplant immunosuppressive therapy consisted of corticosteroids (1 mg/kg twice a day), basiliximab (D0 and D4 post-transplant) and tacrolimus. She suffered from severe acute liver inflammation, predominantly affecting the centrilobular area, which was considered as an acute rejection and treated accordingly with corticosteroid boluses, rituximab and anti-thymocyte globulins. MMF, which is commonly used to manage recurrent AIH post-transplant, was added to tacrolimus due to the possibility that the observed inflammation could rather reflect AIH recurrence on the graft [28]. Two years after her liver transplantation, she developed autoimmune hemolytic anemia that responded well to rituximab and corticosteroids. She subsequently received two additional doses of rituximab in the context of recurrent liver cytolysis, combined with liver histology showing signs of chronic active hepatitis. She also developed secondary hypogammaglobulinemia after rituximab therapy that required Ig replacement. MMF was then replaced by sirolimus in addition to tacrolimus due to the recurrence of reticulocytosis, and rituximab therapy was discontinued. Her immunodeficiency genetic panel evidenced heterozygous VUS in *NOD2* (c.549G>*T*) and *CARD11* (c.2735G>*A*). Six years after her liver transplant, she still displays fluctuating liver enzymes, and the reintroduction of rituximab is being considered.

4. Discussion

We present five AIH pediatric cases with an associated phenotype of immune dysregulation. IEI diagnosis was made either before ($n = 2$), concomitantly ($n = 2$) or after ($n = 1$) AIH diagnosis. While only two patients had a confirmed genetic diagnosis of IEI, all patients had clinical presentation compatible with a primary immune regulatory disorder, i.e., displaying AIH with immune-mediated cytopenia and/or immune-mediated skin disease and/or hypogammaglobulinemia, and an early age of onset of immune dysregulation symptoms (less than 5 years old for most patients). In addition to the necessity of monitoring liver enzymes in patients diagnosed with IEI, our small case series underlies the need to actively look for clinical signs of immune dysregulation in AIH patients and to proceed to genetic testing and immune investigations in case of IEI suspicion.

AIH can be atypical in IEI patients, as demonstrated by the relatively low AIH diagnosis scores achieved by our patients when using two different scoring systems [29,30]. However, all our native-liver patients responded very well to immunosuppressive therapy. Four of our patients initially presented with seronegative AIH, a subtype of AIH in which autoantibodies and hypergammaglobulinemia are lacking, making the diagnosis very challenging as liver biopsy and response to immunosuppressive therapy remain the two only reliable disease hallmarks [31]. For this reason, we believe that there should be a low threshold in performing liver biopsy and initiating immunosuppressive therapy in IEI patients with persistent liver cytolysis, especially in patients with antibody deficiencies.

It should be noted that most of the patients described in this work were not treated with conventional AIH therapy, but rather on a case-by-case basis determined by expert opinions instead of guidelines. The coexistence of AIH and IEI is quite rare, and, to date, no clinical guidelines exist to assist in the simultaneous management of both conditions. For example, although azathioprine is a more common treatment for the AIH observed in APECED, there are no existing guidelines and some patients have been treated with MMF as monotherapy – similarly to Patient 4 – or even with MMF in combination with rituximab [19]. Rituximab has been successfully used in AIH patients suffering from concomitant immune disease, with 90 % of complete biochemical response achievement [27]. Interestingly, two of the three patients who received rituximab therapy in our cohort subsequently developed hypogammaglobulinemia, a feature which is classically observed in pediatric patients with IEI [32]. Our center's experience with rituximab in pediatric AIH is encouraging, but the small cohort described in this work confirms that caution is advised when treating patients with possible associated IEI [33]. Most of our patients needed multiple unconventional therapies and/or treatments adjustments during their follow-up, which underlies the challenge of managing AIH-IEI patients and the need to develop dedicated guidelines.

Unexpectedly, Patient 1 did not display the veno-occlusive disease with immunodeficiency syndrome (VODI) classically associated with *SP110* mutation but rather presented with a CVID-like phenotype [34]. Patient 3, on the opposite, suffered from a hepatic veno-occlusive disease (hVOD) that spontaneously resolved before AIH onset, which is interesting as hVOD has not been described in CVID-like phenotypes. Also, APECED-associated hepatitis is sometimes considered a separate entity as this condition displays autoimmune features that can slightly differ from classical AIH [19,35]. Similarly, the line between nodular regenerative hyperplasia and AIH can sometimes be difficult to draw in CVID patients

[36]. Again, liver impairment in IEI is still partially understood, and we believe that prompt diagnosis associated with immune phenotyping and genetic testing will help us to understand this association better.

Our limited case series represents 6 % of our full AIH cohort. Associated extra-hepatic signs of autoimmunity are usually reported in 20–50 % of AIH patients. However, the proportion of immune dysregulation with impaired immune phenotyping and/or genetically confirmed IEI is still unknown in AIH patients [37]. Liver impairment in IEI is complex, and we still have progress to make regarding the early diagnosis of this association and the understanding of its physiopathology. Close collaboration between immunologists, hepatologists and geneticists will be needed to improve our knowledge and provide those patients with the best possible care.

Author contributions

Conceptualization: FA; Data curation: GJ; Writing - original draft: GJ; Writing - review & editing: FT, CT, FA.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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