The Association of Two Rare Diseases is Not Rare: Primary Immunodeficiencies and Autoimmune Liver Diseases

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Abstract

Purpose: PIDs associates with autoimmune diseases include autoimmune liver diseases (AILD); however, the frequency of PIDs among patients with AILD is unknown. This study aimed to evaluate the strength of the association between AILD and PIDs.

Methods: We conducted this single-center, cross-sectional, and descriptive study in a tertiary hospital. We evaluated eighty-two patients with AILD (39 autoimmune hepatitis (AIH), 32 with primary biliary cholangitis (PBC), seven with variant syndromes (VS), and four with primary sclerosing cholangitis (PSC) for the presence of PIDs. We obtained a detailed history of infections, comorbidities, family history, and laboratory data from the files. All patients were evaluated in the immunology department for further examination, and PID diagnoses were made according to ESID (The European Society for Immunodeficiencies) criteria.

Results: Out of 82 patients with AILD, PIDs were diagnosed in 18% (15 patients); there were four patients with common variable immunodeficiency (CVID), four with partial IgA deficiency (PIgAD), four with selective IgM deficiency (SIgMD), and three with combined immunodeficiency (CID). PIDs were present in 29% of patients with VS, 25 % of patients with PSC, 23% of patients with AIH, and 9% of patients with PBC.

Conclusion: Although PIDs are rare diseases in the general population, they have a strong association with AILD and were detected in one-fifth of the patients. Further research with larger patient groups is needed to evaluate the diagnostic and prognostic impacts of PIDs on AILD.

Introduction

The liver drains both caval and portal systems. Therefore, it is exposed to a variety of antigens from the diet, intestinal microbiota, and autoantigens. With such an extensive antigenic stimulus but a limited immunologic response, the liver can be considered a “tolerogen” organ rather than a “reactive” one [1].

In the liver, inherent immune mechanisms balance surveillance with tolerance. Breakdown of balance leads to the development of autoimmune liver diseases (AILD) such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and variant syndrome (VS) [2]. Our knowledge regarding the pathogenesis of loss of self-tolerance is limited to some molecular and cellular mechanisms like Kupffer and T regulatory cell dysfunctions and altered gut-liver axis and remains to be elucidated [3].

Primary immunodeficiencies (PIDs) are a rare and heterogeneous group of genetic disorders that affect the development or function of the immune system [4]. More than 450 genes that cause PIDs have been identified until now [5]. PIDs’ clinical presentations are not limited to infections but also include allergy, lymphoproliferation, autoinflammation, and autoimmunity as other manifestations of immune dysregulation [6]. The rate of autoimmune diseases in PIDs is reported to be 26.2% [7]. Along with other

autoimmune diseases, AILD is also frequent in PIDs [8–10]. Therefore, immune dysregulation in AILD may be caused or aggravated by underlying PIDs in a subgroup of patients. However, the prevalence of PIDs among patients with AILD is unknown.

Our hypothesis is that PIDs can be a part of immune dysregulation in AILD; therefore, the frequency of PIDs among AILD patients is higher than the general population. We aimed to test our hypothesis by determining the frequency of PIDs in established AILD. Elucidating the association of AILD and PID will pave the way for a better understanding of AILD pathophysiology and the definition of individualized therapeutic options.

Methods

We conducted this single-center, cross-sectional and observational study at Hacettepe University Faculty of Medicine Hospital, Gastroenterology Unit, and Pediatric Immunology units between January and July 2020. We included the patients older than 18 years who met current AIH, PBC, PSC, or VS criteria, with stable doses of drug treatment for the last three months, and who gave informed consent. For AIH criteria, we accepted The International Autoimmune Hepatitis Group (IAIHG) score of at least 12 [11]. For PBC and PSC criteria, we used the current AASLD guidelines [12, 13]. We used the Paris criteria for AIH and PBC variant [14]. Since there was no international guideline for diagnosing the OIH and PSC variant, we decided according to the patient's clinical and laboratory findings. Exclusion criteria were the presence of concomitant liver diseases, acute decompensation of liver disease or acute on chronic liver disease, active chemotherapy, or hematopoietic stem cell transplantation. We interviewed patients by using the PID screening questionnaire of the Modell Jeffrey institution [15]. We also obtained a detailed history, including past infections, comorbidities, and family history. Recent laboratory data were collected from the hospital electronic database, includes complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), direct and indirect bilirubin, albumin, prothrombin time (PT) and international normalized ratio (INR), activated partial thromboplastin time (aPTT), creatinine, urea, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (Anti-HBs), Hepatitis B core antibodies (anti-HBc IgG and IgM), Hepatitis C Antibody (Anti-HCV), Anti-Human Immunodeficiency Virus (Anti-HIV) anti-hepatitis A virus antibody (Anti-HAV total), antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), liver kidney microsomal antibody type 1 (LKM-1), immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), immunoglobulin gE (IgE), complement 3 (C3), complement 4 (C4), hepatobiliary ultrasound (US), and upper abdomen magnetic resonance imaging (MRI). The clinical and laboratory evaluation of all patients was done in the pediatric immunology department. The PID diagnosis depended on the ESID (The European Society for Immunodeficiencies) criteria [16].

Results

We identified 111 AILD patients through our study period. Among them, nine patients did not give informed consent, six patients' diagnoses did not meet the current diagnostic criteria of each AILD, three

patients have acute liver decompensation, two patients were on active chemotherapy, one patient has accompanying Wilson disease, one patient has hematopoietic stem cell transplantation due to lymphoma. The remaining 89 patients, including 43 AIH, 32 PBC, 6 PSC, and 8 VS, were included in the study. PIDs could not be excluded in seven patients (4 AIH, 2 PSC, and 1 VS) by initial evaluation, and it was planned to monitor them in terms of PIDs and complete evaluation after the COVID-19 pandemic. Out of the remaining 82 patients who completed the PID evaluation, PIDs were detected at 18% (15 patients) of AILD (Fig. 1). There were four (4.8%) patients with common variable immunodeficiency (CVID), four (4.8%) patients with partial IgA deficiency (PIgAD), 4 (4.8%) patients with selective IgM deficiency (SIgMD), and three (3.6%) patients with combined immunodeficiency (CID). PIDs were detected in 29% of VS (2/7 patients; 1 CID and 1 CVID); 25% of PSC (1/4 patient; 1 SIgMD); 23% of AIH (9/39 patients; 4 PIgAD, 3 SIgMD, and 2 CVID) and 9% of PBC (3/32 patients; 2 CID and 1 CVID). While four patients with CVID were previously diagnosed, all other patients with PID were diagnosed during this study. All CVID patients were on monthly IVIG treatment, and their liver diseases were in remission.

The demographic and clinical features of AILD patients with and without PIDs were summarized in Table 1. There were no significant differences between groups for age, gender, age at diagnosis of AILD, presence of cirrhosis, and treatment response to AILD. The frequencies of autoimmunity or malignancy accompanying AILD, familial history of autoimmunity or malignancy, and parental consanguinity were also similar among patients with and without PIDs. Patients with PID were younger (37 vs. 49 years of age, p = 0.054). Their thrombocyte counts were lower (217 vs. 260/ml, p = 0.013), while patients without PID had higher GGT (115 vs. 68 IU/L, p = 0.047) and lower serum albumin (4.1 vs. 4.4 mg/dl, p = 0.056) levels. Seronegativity (i.e., ANA, ASMA, and LKM-1 negativity) was higher in AIH patients with PID than in those without PID (22% (2/9) vs. 3% (1/30), p = 0,127). Similarly, AMA seronegativity was also higher in PBC patients with PID (67% (2/3) vs. 14% (4/29), p = 0,083).

Table 1
Demographic and Clinical Features of Patients with AILD

		All patients		with PID		without PID	p-value
	n		n		n		
AILD, n (%)	82	39 (48)	15	9 (60)	67	30 (45)	0.405
• AIH		32 (39)		3 (20)		29 (43)	
• PBC		4 (5)		1 (7)		3 (5)	
• PSC		7 (9)		2 (13)		5 (7)	
• VS							
Female, n (%)	82	64 (78)	15	11 (73)	67	53 (79)	0.980
Median age, years (min-max)	82	49 (18–75)	15	37 (19–60)	67	49 (18–75)	**0.054**
Median age at diagnosis of AILD, years (min-max)	82	45 (6–72)	15	34 (9–60)	67	45 (6–72)	0.128
Extrahepatic autoimmunity, n (%)	82	28 (34)	15	5 (33)	67	23 (34)	1.000
Malignity, n (%)	82	7 (9)	15	1 (7)	67	6 (9)	1.000
Parental consanguinity, n (%)	82	23 (28)	15	4 (27)	67	19 (28)	1.000
Autoimmunity in family, n (%)	82	26 (31)	15	7 (47)	67	19 (28)	0.221
Malignity in family, n (%)	82	27 (33)	15	6 (40)	67	21 (31)	0.552
Cirrhosis, n (%)	82	10 (12)	15	2 (13)	67	8 (12)	1.000
Hepatomegaly, n (%)	82	18 (21)	15	5 (33)	67	13 (21)	0.335
Splenomegaly, n (%)	82	21(26)	15	7 (46)	67	14 (23)	0.102

Statistical analysis is done between with and without PID groups.

AIH, autoimmune hepatitis; AILD, autoimmune liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dl, deciliter; g, gram; GGT, gamma-glutamyl transferase; INR, international normalized ratio, L, liter; mg, milligram; n, sample size; PBC, primary biliary cholangitis; PID, primary immunodeficiency; PSC; primary sclerosing cholangitis; U, unite; VS, variant syndrome

		All patients		with PID		without PID	p-value
Treatment response, n (%)	82	6 (7)	15	1 (7)	67	5 (7)	0.762
• New diagnoses		68 (83)		11 (73)		57 (85)	
• Sufficient		8 (10)		3 (20)		5 (7)	
• Insufficient							
Hemoglobin (g/dl) (min-max)	71	13.0 (8.1–17.0)	14	13.5 (9.4–16.7)	57	12.9(8.1–17.0)	0.278
Leukocyte (/ml) (min-max)	71	6.9 (3.5–14.3)	14	6.0 (4.1–10.8)	57	6.9 (3.5–14.3)	0.552
Neutropenia (< 1,5 x10^3/ml), n (%)	71	2 (3)	14	1 (7)	57	1 (2)	0,358
Lymphopenia (< 1,3 x103/ml), n (%)	71	7(9)	14	1 (7)	57	6 (11)	1,000
Thrombocyte(/ml) (min-max)	71	247 (73–494)	14	217 (84–286)	57	260 (73–494)	**0.013**
AST (IU/L) (min-max)	71	64 (18-11179)	14	69 (26–409)	57	64 (18-11161)	0.768
ALT (IU/L) (min-max)	71	74 (12-2126)	14	74 (12-2126)	57	111 (25–437)	0.501
GGT (IU/L) (min-max)	71	108 (18–606)	14	68 (18–325)	57	115 (18–606)	**0.047**
ALP (IU/L) (min-max)	71	165 (62-2014)	14	167 (75–410)	57	163 (62-2014)	0.334
Albumin (mg/dl) (min-max)	71	4.2 (2.4–4.9)	14	4.4 (3.6–4.7)	57	4.1 (2.4–4.9)	0.056
T. Bilirubin (mg/dl) (min-max)	71	0.6 (0.2–24)	14	0.7 (0.3–2.4)	57	0.6 (0.2–24)	0.783
INR (min-max)	71	0.9 (0.7–2.1)	14	0.9 (0.7–2.1)	57	1 (0.8–1.4)	0.543
Creatinine (mg/dl) (min-max)	71	0.6 (0.2–0.9)	14	0.5 (0.2–0.9)	57	0.6 (0.2–0.9)	0.194

Statistical analysis is done between with and without PID groups.

AIH, autoimmune hepatitis; AILD, autoimmune liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dl, deciliter; g, gram; GGT, gamma-glutamyl transferase; INR, international normalized ratio, L, liter; mg, milligram; n, sample size; PBC, primary biliary cholangitis; PID, primary immunodeficiency; PSC; primary sclerosing cholangitis; U, unite; VS, variant syndrome

The annual rate of upper respiratory tract infections was significantly higher in patients with PIDs (73% vs. 34%, p = 0.013) (Table 2.). The history of frequent upper respiratory tract infections (≥ 4 times in a year) was 20% in PID patients, while only 9% in those without PIDs. Additionally, the annual rate for pneumonia was significantly higher in PID patients (48% vs. 7%, p = 0.001). On the other hand, infection rates for herpes, warts, and fungal were similar between patients with and without PIDs.

Table 2
History of infections in AILD patients according to the presence of PIDs.

	with PID **n = 15**	**without PID** **n = 67**	**p-value**
Parenteral antibiotic use n (%)	3 (20)	7 (47)	0.380
Upper respiratory tract infection, n (%)	11 (73)	23 (34)	**0.013**
• ≥ 1 time(s) in a year	3 (20)	6 (9)	*
• ≥ 4 times in a year			
Pneumonia (≥ 1 time in life), n (%)	7 (48)	5 (7)	**0.001**
Labial herpes, n (%)	5 (33)	22 (33)	1.000
• ≥ 1 time(s) in a year	2 (13)	3 (5)	*
• ≥ 4 times in a year			
Warts (≥ 1 time(s) in life), n (%)	3 (20)	8 (12)	0.414
Fungal infection (≥ 1 time(s) in life), n (%)	4 (27)	12 (18)	0.477
*Statistical analysis could not be made due to the low number of observations.			

Discussion

In this study, PIDs were detected in 18% of AILD patients. In patients with AILD and PIDs, lower and upper respiratory tract infections were more frequent. Although immune dysregulation in patients with PID makes them prone to autoimmunity, to the best of our knowledge, there is no research on the prevalence of PID in AILD patients in the literature.

Previous data regarding the association of AILD with PID limited to studies that investigate the frequency of autoimmune diseases in PID cohorts. In these studies, AIH was reported at a range of 1.6–43.0% in different PID syndromes [17–21]. PBC was detected in %1.2 of patients with CVID [22]. PSC accompanied various types of PIDs in children [23] and was present as high as % 45 of patients with hyper immunoglobulin M syndrome [24]. The prevalence of PIDs in the general population is estimated to be 1:10.000 but may be more frequent in populations with common consanguineous marriage [25, 26]. As

such, it is estimated that PID prevalence is relatively higher in Turkey, with 24% consanguineous marriage in 2008 [27–29]. This is the first study investigating the frequency of PIDs among AILD, and PIDs were found in 18% (15/82) of AILD patients, which was significantly higher than estimations for the general population.

Concomitant PID and AILD is a challenging diagnosis. Because of the changes in immunological parameters, such as autoantibody titers and Ig levels. There are several case reports emphasizing the difficulties in diagnosing AIH with standard diagnostic criteria due to low immunoglobulin levels in CVID patients [30–32]. Furthermore, Fukushima et al. suggested that some CVID cases reported as “non-B non-C hepatitis” who benefited from immunosuppressive therapy may have had AIH [30]. Similarly, some cases were described in the literature as “chronic hepatitis” accompanying CVID [33], and those may actually be undiagnosed AIH patients with accompanying PID. In our study, seronegativity rates among AIH and PBC patients were higher in the PID group than in the group without PID; however, this difference remained statistically insignificant due to the low number of observations. On the other hand, the diagnosis of PIDs may be overlooked in AILD patients since the increased frequency of infection is attributed to immunosuppressive treatment. Indeed, most of the patients with PID were diagnosed during this study, except for four patients previously diagnosed with CVID.

We do not know the effects of underlying PIDs on the prognosis and course of AILD. The increased frequency of infections in cirrhotic AILD patients with PIDs may accelerate their transition from compensated to decompensated state. PIDs may further increase the risk of infection in liver transplant recipients. In this study, upper respiratory infections and pneumonia were more common in PID patients than without PIDs, while viral and fungal infection rates were similar. The predominance of bacterial infections rather than viral infections can be explained by the fact that most AILD patients with PIDs patients had antibody deficiencies. The effect of PID-associated infections could not be examined since patients with decompensated cirrhosis were excluded from the study. Additionally, there was no difference in the rates of compensated cirrhosis and treatment unresponsiveness between patients with and without PID. Nevertheless, it may be due to the small number of patients included in the study.

An important question arises on which AILD patients should be investigated for PIDs. The literature points out frequent or atypical infections, autoimmunity, lymphoproliferative diseases, family history, and parental consanguinity as warming factors to investigate PIDs in the general population [34]. We suggest that at least AILD patients with a history of frequent or severe infections should be evaluated for the associated PIDs.

To the best of our knowledge, this study is the first study that investigates the frequency of PIDs in AILD. The significantly higher frequency of PIDs among AILD than the general population and the lack of awareness about investigating PIDs in AILD has been revealed. However, there are some limitations. First, this is a single-center study, and the number of patients, especially PSC patients, was limited. Therefore, besides infections, we could not identify other warning parameters for PIDs. Secondly, the impact of PIDs on the diagnosis and prognosis of AILD could not be defined. Lastly, genetic analysis and

histopathological evaluation could not be performed in order to investigate the possible mechanisms of interaction between immunodeficiency and autoimmunity in the liver. Further research with larger patient samples from multiple centers is needed to evaluate the prevalence of PIDs and their clinical impacts on AILD. In addition, histopathological and genetic studies are needed to better understand immune dysregulation in AILD patients with PID. These studies not only will better characterize and classify AILD by facilitating diagnosis and predicting prognosis, but they can also pave the way for targeted therapy in AILD patients.

Conclusions

Although PIDs are rare in the general population with a total estimated prevalence of 1 in 10000, we concluded that it is more frequent (18%) in AILD patients. This is the first study that points to the underdiagnosis of PIDs among patients with AILD. More studies are needed to reveal the prevalence and clinical implications of PID in AILD patients and to develop new individualized treatment options.

Declarations

Funding:

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Conflicts of Interest:

The authors declare that there is no conflict of interest.

Availability of data and material:

Not applicable

Code availability:

Not applicable

Authors' contributions:

ŞNA- study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; ES, CŞ- study concept and design; acquisition of data; analysis and interpretation of data; assistance in manuscript preparation and revisions; DÇ, YB- study concept and design, interpretation of data, study supervision, manuscript preparation and revisions.

Ethics approval:

The local ethics committee of Hacettepe University approved the study (study approval identification code: GO 19/1122).

Consent to participate:

Written informed consents were obtained from all participants.

Consent for publication:

All authors provided consent for publication.

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Figures

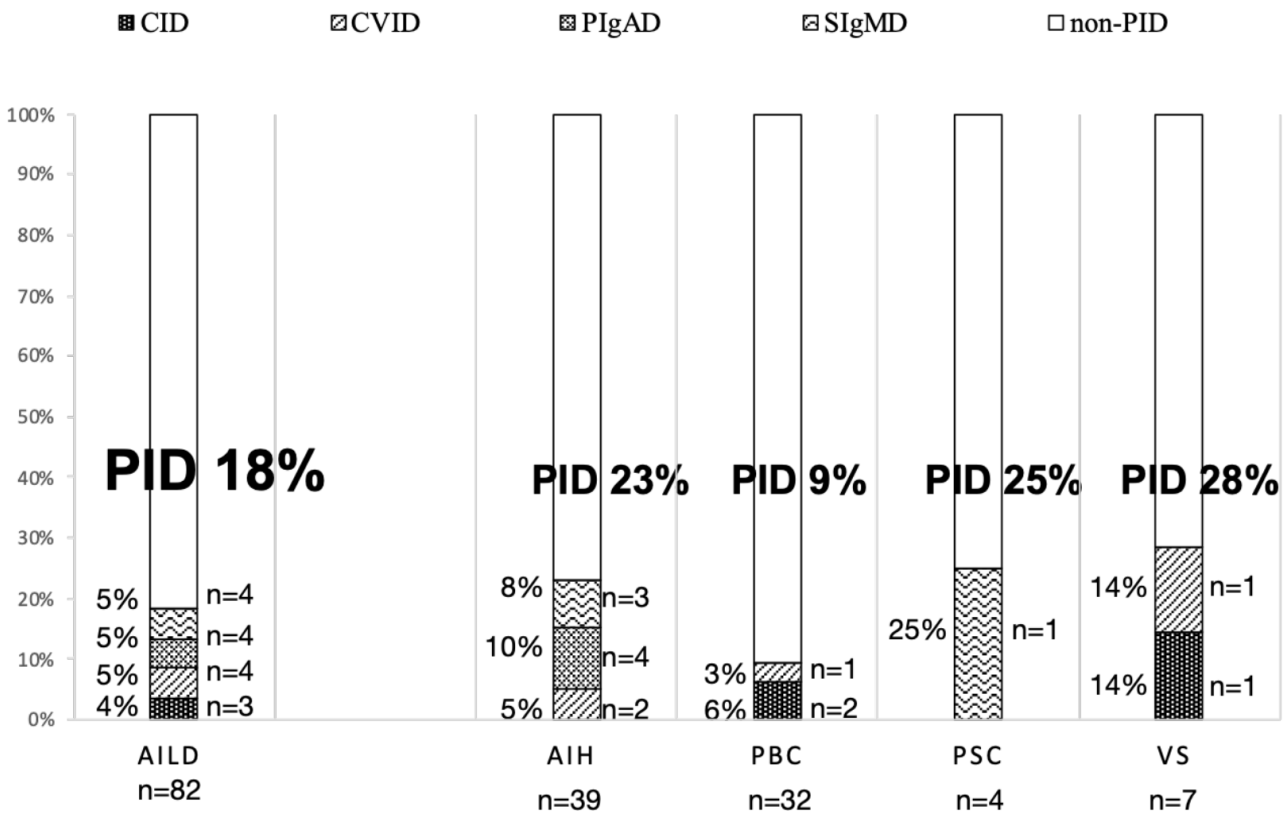

Figure 1

Frequency and distribution of PIDs in AILD groups PIDs were detected in 18% of all AILD (15/82 patients; 4 CVID, 4 PIgAD, 4 SIgMD and 3 CID); 23% of AIH (9/39 patients; 4 PIgAD, 3 SIgMD, and 2 CVID); 9% of PBC (3/32 patients; 2 CID and 1 CVID); 25% of PSC (1/4 patient; 1 SIgMD) and 29% of VS (2/7 patients; 1 CID and 1 CVID). AIH, autoimmune hepatitis; AILD, autoimmune liver disease; CID, combined immunodeficiency; CVID, common variable immunodeficiency; PBC, primary biliary cholangitis; PID, primary immunodeficiency; PSC; primary sclerosing cholangitis; VS, variant syndrome.