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Research Article

Clinical and immunological phenotypes in autoimmune hepatitis - our experience

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Abstract. Objective: Autoimmune hepatitis (AIH) is a rare, autoimmune disease of the liver, with very variable clinical presentation, encountered mainly in young women.The aim of our study was to make a diagnostic approach in typical and atypical AIH cases and assess the clinical phenotypes and immunological features. Material and Method: We performed a retrospective study of the medical charts of 56 patients with AIH (ranging from 20-73 years old) – diagnosed in a tertiary care teaching hospital. Results: We enrolled 56 patients (40 females and 16men), 40 of 56 patients had another coexisting autoimmune disease. All patients were diagnosed with AIH type1; the presence of ANA (speckled pattern) was predominant. In 8.92% (5/56) patients there were no antibodies detected. Only 6/20 patients had higher values of IgG. 75% of our patients were symptomatic, and 7.41% had cirrhosis. Half of the clinical complaints were difficult to be classified as AIH, as these subjects had also another autoimmune condition. Coexistence of other autoimmune diseases was present in a higher percentage (71.42%), but negative phenotypes in a lower percentage (8.92%) compared to other authors. Conclusion: Many cases previously classified as cryptogenic hepatitis could be actually AIH. Especially in females with another preexisting autoimmune disease, simplified criteria of the International AIH Group allows the certain diagnosis of AIH.

Key Words: autoimmunity; hepatitis; phenotype; antibodies; chronic liver disease

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Background

Autoimmune hepatitis (AIH) is a chronic, autoimmune disease of the liver, which affects classically mainly young white women (Czaja et al 2016); although it is a rare disorder, its trend to increasing incidence represents a serious burden for medical finances (Hirode et al 2020). Its prevalence is variable, ranging from 15-25/100.000 inhabitants (Europe) to 43/100.000 (Alaska). The two peaks of the debut of AIH are at teenage and about 40-60 years (Srivastava et al 2010).

Clinical presentation is very variable, fluctuating and includes the acute form with negative autoantibodies, ranging from asymptomatic patients to overt hepatic encephalopathy, while other cases present acute exacerbation of chronic AIH (Mack et al 2020). The increasing trend of acute AIH has been shown by Takahashi et al 2020. Physical examination shows a broad range of features, from no change to signs of chronic liver disease or even portal hypertension.

Immunological diagnosis is based on antibodies detection, among which antinuclear antibody (ANA) in a titer over 1:80 (adults) and 1:40 (children), anti-smooth muscle antibody (SMA) in titer over 1:100, anti-liver-kidney microsomal antibody (LKM) in a titer over 1/40 (Dalekos et al 2019).

From an immunological point of view, there are several types of AIH; AIH type 1 (90%) which can be encountered at any age, but mainly in young women, with variable clinical picture and positive ANA, SMA, antibodies against soluble liver antigen (SLA) and hypergammaglobulinemia. AIH type 2 (10%) is found especially in males, children and young adults, with positive LKM1-antibodies. Seronegative AIH (negative ANA, SMA or LKM1) is characterized by positive p-ANCA, antibodies against actin, LKM3-antibodies (Mack et al 2020).

The aim of our study was to evaluate the patients admitted with typical and atypical AIH and assess the clinical phenotypes and immunological features in a retrospective 4-year-study.

Materials and methods

We performed a retrospective study of the medical charts of patients with AIH – diagnosed in a tertiary care teaching hospital – admitted in the Internal Medicine Department between 2016-2020.

All included patients underwent clinical, biological and ultrasonographical examination and 7/56 (12,5%) patients had also histological examination. All patients with immunological criteria (autoantibodies > 1:80) and/or histological confirmation of AIH were included. Patients having other autoimmune hepatic diseases: primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), overlap syndromes (AIH+PBC, AIH+PSC), or viral hepatitis (HAV, HBV, HCV) were excluded. ANA titers were measured using a standard indirect immunofluorescence technique.

All patients included have signed the informed consent and also the approval for participating in medical teaching, in accordance with the Declaration of Helsinki.

Statistical analyses were performed using descriptive statistics. All categorical variables are expressed as proportions (%).

Results

A total of 56 patients, ranging from 20 to 73 years old, were included. Demographics and baseline characteristics of subjects included are listed in Table 1.

Table 1. Demographics and baseline characteristics of subjects (n=56)

Age (years) mean ± standard deviation	51.5 ± 11.59	n%
	20-29	3 (5.35)
	30-39	9 (16.07)
	40-49	10 (17.85)
	50-59	22 (39.28)
	60-69	8 (14.28)
	>70	4 (7.14)
Gender	Male	16 (28.57)
	Female	40 (71.42)
Provenience	Urban	45 (80.35)
	Rural	11 (19.64)
BMI (kg/m^2) (mean ± standard deviation)	<23 (%)	1 (1.78)
	≥23 and < 25 (%)	33 (58.92)
	≥25 (%)	22 (39.28)
Simplified AIH score	3	3
	4	36
	5	5
	6	10

AIH – autoimmune hepatitis;

BMI – Body mass index

We analyzed also the co-existence of other autoimmune diseases, and this was observed in 40 patients (71.42%): systemic lupus erythematosus (12.5%), Sjogren syndrome (5.35%), Basedow disease (3.57%), Hashimoto thyroiditis (16.07%), scleroderma (7.14%), rheumatoid arthritis (8.92%), anchylosing spondylitis (3.57%), dermatomyositis (5.35%), Raynaud syndrome (7.14%), mixed connective tissue disease (7.14%), anti-phospholipidic syndrome (5.35%), vasculitis (3.57%), sacroiliitis/seronegative spondylarthropathy (8.92%), diabetes mellitus type 1 (3.57%), psoriasis (3.57%), coeliac disease (1.78%), ulcerative colitis (1.78%), autoimmune thrombocytopenia (8.92%), telangiectasis (5.35%). Of these 40 patients, 25 patients had one associated autoimmune disease, 9 had two, 5 had three and 1 had more than 3 associated autoimmune diseases.

The reasons of admittance in our department consisted in: inflammatory type of polyarthralgia (n=19; 16 of them had another autoimmune diseases), asthenia and fatigue (n=19, but 10/19 had other comorbidities), right upper quadrant pain (n=9), weight loss (n=7), Raynaud syndrome (n=4; 2 of them had also scleroderma) myalgia (n=4; 2 of them had also myositis), loss of appetite (n=5), xerostomia (n=3, 2 of them had also Sjogren syndrome), maculopapular rash (n=1) and jaundice (n=1).

Laboratory data showed a mild hepatic cytolysis with an average value of 54.81 U/l for glutamic-pyruvic transaminase (GPT) and 51.40 U/l for glutamic oxaloacetic transaminase (GOT).

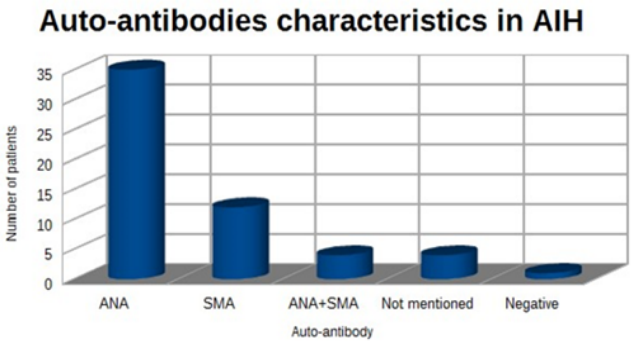


Figure 1. Immunological characteristics of included patients

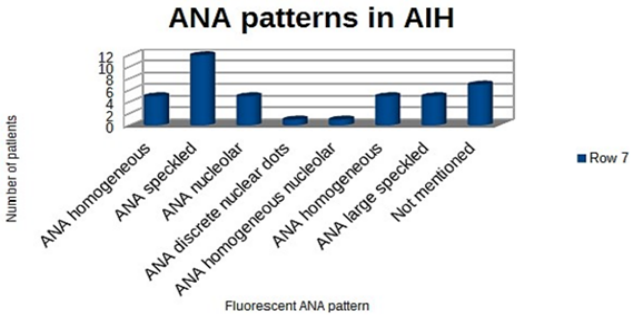


Figure 2. ANA patterns in AIH

All our patients were diagnosed with AIH type 1; the presence of ANA and the speckled ANA pattern were predominant, as seen in Figures 1 and 2. In 8.92% (5/56) patients there were no antibodies detected. In only 6/20 patients with IgG plasma levels evaluated, had higher values of IgG and only half of the patients had hypergammaglobulinemia.

Applying the simplified score system, most of our patients (46/56) fulfilled the criteria of possible AIH (scores 3, 4 and 5) and only 10/56 the one of probable AIH (score 6), as seen in Table 1.

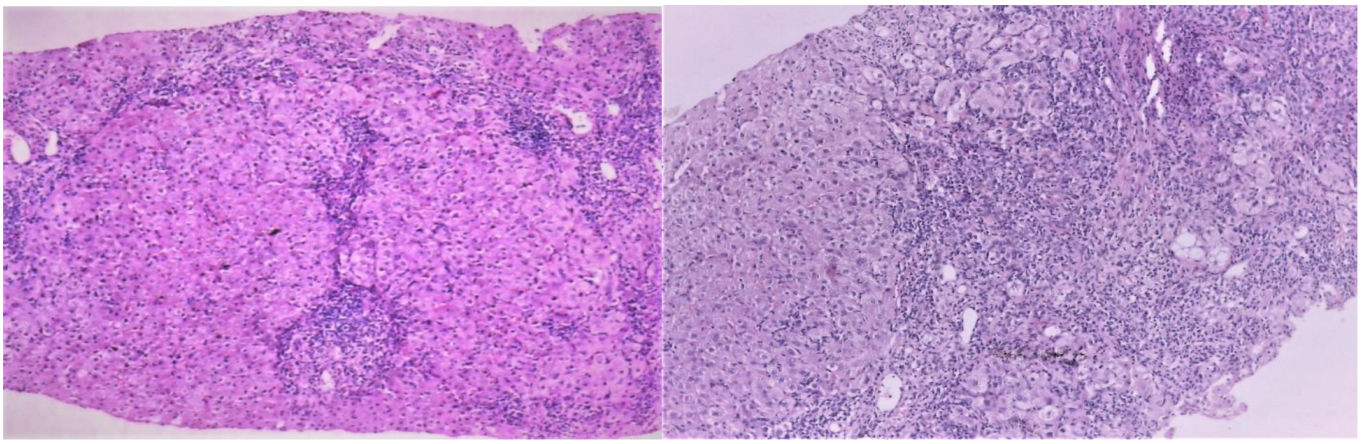
Regarding the ultrasonographic features, 29/56 (51.78%) had steatosis, 12/56 (21.42%) hepatomegaly, 37/56 (66.07%) homogeneous structure, and 11/56 (19.64%) inhomogeneous granular hepatic structure, 8/56 (14.28%) normal aspect and 3/56 (5.35%) cirrhosis.

Follow-up at 4 years after the initial AIH diagnosis revealed progression to cirrhosis in 8 patients (14.28%) although the patients were on treatment. All those 8 patients were females and they have also associated autoimmune diseases (4 systemic lupus erythematosus, 2 Hashimoto thyroiditis, 1 mixed connective tissue disease, 1 rheumatoid arthritis).

Histological findings in our 7 cases that underwent liver-biopsy consisted in: interface hepatitis (all cases), lobular hepatitis (5/7), lymphocytic inflammatory infiltration (6/7), hepatocyte rosettes (3/7) and emperipolesis (1/7), as seen in Figure 3.

Complete remission (biochemical and immunological) was observed in 28 patients (50%). Patients in this group have all received treatment: 24 patients received corticotherapy (1mg/kg/day Prednison at beginning and 10mg/day chronic dose) + azathioprine (1 mg/kg/day), while 4 patients received just corticotherapy.

Persistent AIH (cytolysis, positive ANA or SMA) was found in 10 women, despite the treatment received (corticotherapy + azathioprine). There were also drop outs, 10 patients of the initial



a) b)

Figure 3. Histological features in a 56-year-old woman with AIH (hematoxylin and eosin): (a) portal lymphocytic inflammatory infiltration (magnification×4) and (b) interface hepatitis (magnification×10)

group did not return to 1 year follow-up scheduled visit, because of lack of compliance (6) and due to moving to another city (4).

Discussion

The prototype of our AIH subject consisted in female patients living in urban area, most of them having atypical symptoms and another systemic autoimmune disease, with positive immunological markers.

The majority (71.42%) of the group included in our study were females, similar to classical literature data (Czaja et al 2016). Although, nowadays any age or gender, ethnic groups or even patients with acute or chronic hepatitis of undetermined cause should be suspected of AIH (Czaja et al 2016). One hypothesis explaining the large amount of patients of urban origin (80.35%) diagnosed with AIH could be the higher exposure rate to external trigger factors, especially to stress, compared to those from rural origin or the higher accessibility to medical resources in comparison to the rural patients; the involvement of psychological stress in the relapse of type 1 AIH has been described by Srivastava S et al. (Srivastava et al 2010).

The diversity of clinical manifestation complicates the diagnosis and management of this pathology. Nonspecific, insidious onset of symptoms, such as fatigue, mild right upper quadrant pain, weight loss, nausea, jaundice, extrahepatic manifestations (arthralgia, myalgia), unexplained fever, or amenorrhea were the only clinical manifestations in 1/3 of patients (Mack et al 2020). In 42 of the 56 patients (75%) there were symptoms present at their first admission, suggesting a slightly lower percentage (25%) of the asymptomatic patients, in comparison to data reported in literature (33,3%) (Dalekos et al 2019). Half of the clinical complaints of our patients (Raynaud Syndrome, asthenia, fatigue, myalgia, weight loss) and even more (84.21% patients) in cases of inflammatory polyarthralgia were difficult to be classified as belonging to AIH, as these subjects had also another autoimmune condition, that could have given these symptoms. Although jaundice was mentioned in 10% patients as one of the most common liver-specific finding (Tunio et al 2021), only 1.78% of our patients presented this sign.

Pryce CR et al. reported that 1/3 of patients are diagnosed already in stage of cirrhosis, mostly in extreme age (Pryce et al 2017). It is possible that due to early presentation, only 4/56 (7.41%) of our patients to have had esophageal varices and an ultrasonographical pattern of cirrhosis. The prevalence of co-existing steatosis was 51.78%, much higher compared to data in literature (33.2%) (Chalasani et al 2020), whereas normal echostructure in 14.28% represented a challenge for our diagnostic pathway.

As a potential diagnostic pitfall at presentation, one should always take into account the possibility of AIH, among other differential diagnosis (Table 2).

Table 2. Possible differential diagnosis of AIH

1.Chronic viral hepatitis B and C
2.Nonalcoholic fatty liver disease
3.Alcoholic liver disease
4.Drug-induced hepatitis (acetaminophen, painkillers, NSAIDs, methotrexate, statins, Amoxicillin-clavulanate,Tetracyclines, Erythromycin, Halothan, Amiodarone, contraceptive pills)
5.Primary biliary cirrhosis
6.Primary sclerosing cholangitis
7.Wilson's disease
8.Hemochromatosis

The coexistence of other autoimmune extrahepatic diseases was present in our study in a higher percentage- 71.42% (40/56 patients) compared to the ones previously reported (14-44%) (Mack et al 2020).

The phenotype with negative autoantibodies has been described and reported to be up to 20%, so the absence of antibodies does not preclude the diagnosis of AIH. Our study revealed a lower percentage (8.92%) of negative phenotypes compared to other authors (20%) (Mack et al 2020) and the amount would have been even lower if non-standard autoantibodies would have been determined and if another method except the standard indirect immunofluorescence technique would have been used for ANA detection (enzyme immunoassay (EIA) or enzyme linked immunosorbent assay (ELISA). There exist also other markers, not completely revealed yet, which are able to diagnose AIH

especially in phenotypes with negative auto-antibodies, such as serum amyloid A1, revealed by proteomic analysis (Wang et al 2020). Acute-onset type of AIH is characterized by lack of typical serological hallmarks of AIH (auto-antibodies, elevated IgG) (Komori et al 2021).

We found a high variability of transaminase levels at our patients, normal and borderline values representing a challenging aspect in establishing the diagnostic algorithm, similar to data in literature; an increased GOT/GPT ratio >1 in acute forms suggests aggressive clinical course of AIH (Ferrari et al 2004). Our 5 ANA-negative patients (4 women, 1 man) presented in all cases as acute forms of hepatitis, with normal serum immunoglobulin G levels, cholestasis and elevated transaminases comparable to the data from literature (Ferrari et al 2004).

ANA and SMA are non-disease specific, as they appear also in alcoholism, nonalcoholic fatty liver disease, chronic virus B/C hepatitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC). In immunofluorescence, there are 3 major ANA patterns: nuclear, cytoplasmic and mitotic (Chan et al 2015). Non-standard autoantibodies include: anti-actin (subset of SMA), anti-α-actinin, anti-soluble liver antigen (anti-SLA, high specificity 99%), atypical perinuclear neutrophil antibodies (p-ANCA), anti-asialoglycoprotein receptor (anti-ASGPR, in children), anti-liver cytosol (anti-LC1, in young Europeans) (Czaja et al 2016). Other suggestive criteria for AIH are represented by hypergammaglobulinemia. The level of IgG correlates to the disease's activity and is considered to be one of the parameters (together with normalization of transaminase) guiding the therapy. Only 6/20 of our patients (30%), at which IgG values and proteinogram were evaluated, had higher values of IgG and only 15% (3/20) of them had hypergammaglobulinemia. Unfortunately, when total protein count is within normal range, further assessment of Ig values is not further pursued. This reduced evaluation of immunological analysis is considered to be also, one of the major limitations of our study, similar to other retrospective studies.

A lot of situations lead to different atypical forms of AIH, which can be diagnosed only by using the clinical judgment and histological examination: asymptomatic AIH, acute/fulminant hepatitis, autoantibody negative phenotype, overlap syndromes (cholestasis in absence of classical features of PSC/PSC), drug induced AIH (statins), all graft dysfunctions after liver transplant (de novo, recurrent AIH), overlap with nonalcoholic steatohepatitis (cirrhosis) or HCV hepatitis (ANA-status being useless for differentiation), histologically atypical AIH (good prognosis, good response to immunosuppression) (Aizawa et al 2017). The amount of complete remission in our groups (50%) was lower than the data reported in the literature (84.4%) (Li et al 2016). This may be explained by multiple factors, of which a lower compliance related to long term medication is a major one, being determined by various factors (Muratori et al 2016). Another limitation of our study is represented by the lack of comparative group treated with budesonide and azathioprine which is now considered the frontline therapy for AIH (Lu et al 2018). In our group, cirrhosis at diagnosis (7.4%) was lower compared to literature data (28-33% of AIH) and even the progression of HAI to cirrhosis (14.28%) in our group showed a lower tendency than previous data reported in the literature (20%) after 4 years of followup (Mack et al 2020). Although Rathi et al described that previous treatment with interferon for viral hepatitis could trigger AIH (Rathi et al 2015), we could not identify any situation with antiviral treatment in patient's history; nor did we include overlap syndromes AIH-viral hepatitis in our study.

Invasive diagnostic methods often represent an obstacle in diagnostic workup, as many patients refuse to undergo liver biopsy, which still remains the gold standard in liver diseases, interface hepatitis being the histological hallmark of AIH (Jabłońska et al 2019).

Conclusion

AIH is an exclusion diagnosis, as typical findings are missing. Many cases previously classified as having cryptogenetic hepatitis could be actually part of AIH. Definite and probable criteria, but also simplified diagnostic criteria (AIH-score-calculator on Internet https://www.mdcalc.com/simplified-autoimmune-hepatitis-aih-score) for the diagnosis of AIH have been established by the International AIH Group.

Especially in female patients with another preexisting autoimmune disease, simplified criteria of the International AIH Group facilitates the diagnosis of AIH.

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