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CASE REPORT

Autoimmune hepatitis in patients with multiple sclerosis: The role of immunomodulatory treatment

Eirini I. Rigopoulou[a,b], Sofia Gyftaki[a], Pinelopi Arvaniti[a,b], Vana Tsimourtou[c], George K. Koukoulis[d], Georgios Hadjigeorgiou[c], George N. Dalekos[a,b,*]

[a] *Institute of Internal Medicine and Hepatology, Larissa, Greece*
[b] *Department of Medicine and Research Laboratory of Internal Medicine, University Hospital of Larissa, Larissa, Greece*
[c] *Department of Neurology, School of Medicine, University of Thessaly, Larissa, Greece*
[d] *Department of Pathology, School of Medicine, University of Thessaly, Larissa, Greece*

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Abstract
Background: Development of autoimmune hepatitis (AIH) has been sporadically reported in patients with multiple sclerosis (MS) either concurrently or after treatment with immunomodulatory drugs, including interferon-beta (IFN-β) and steroids.
Aim: To report a large cohort of 14 patients with MS diagnosed with AIH during an assessment of deranged liver function tests (LFTs).
Patients and methods: From 2005 to 2017, we prospectively identified 14 (13 women) patients with MS who suffered also from AIH after investigation in our department for the presence of deranged LFTs. Age at diagnosis of MS was 36.7 ± 9.3 years while at diagnosis of AIH 43.1 ± 12 years.
Results: AIH diagnosis was based on elevation of aminotransferases in all patients [alanine aminotransferase: 520 IU/L (range: 115—1219)], elevation of IgG in 6, compatible autoantibody profile in all, including 5 patients with liver-specific autoantibodies and typical or compatible histological features in 11 patients. 5 patients were under treatment with IFN-β plus methylprednisolone pulses, 3 with IFN-β plus oral steroids, 1 with IFN-β, 4 with methylprednisolone pulses whereas 1 patient was free of treatment. The median time from IFN-β initiation to the development of hepatitis was 12 months (range:1—120). Treatment for AIH was initiated in 13 patients with prednisolone (0.5—1 mg/kg/day) plus mycophenolate myfetil (2 g/day) in 10 and prednisolone plus azathioprine in 3 with complete and partial response in 11 and 2 patients, respectively.

* Corresponding author at: Department of Medicine and, Research Laboratory of Internal Medicine, University Hospital of Larissa, 41110 Larissa, Greece.
E-mail address: georgedalekos@gmail.com (G.N. Dalekos).

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Conclusions: The differential diagnosis of hepatitis in MS patients should include AIH and in particular when immunomodulatory treatment has been preceded. Autoantibody testing and liver histology play fundamental role in establishing a prompt diagnosis of AIH in these patients. Treatment of AIH in patients with MS seems safe and efficient as complete or partial response was recorded in all of our patients.

Introduction

Autoimmune hepatitis (AIH) is a relatively rare acute or chronic liver disease of unknown aetiology characterized by hypergammaglobulinaemia, circulating autoantibodies and interface hepatitis in liver histology [1—3]. Its pathogenesis combines strong genetic susceptibility and triggers that can direct aberrant T-cell responses against liver antigens. Under this context, microbial or viral pathogens have been implicated in the loss of immune tolerance, which is aggravated by the presence of impaired regulatory mechanisms [4,5]. In addition, AIH may be developed after the administration of several drugs, herbals and biologic agents [2,3,6—9]. Therefore, the diagnosis of AIH can often pose difficulties and its differential diagnosis can be challenging, as clinical and histological overlap can exist between drug-induced liver injury (DILI) and DILI-induced AIH [2,3,10,11].

On the other hand, multiple sclerosis (MS) is a chronic, autoimmune demyelinating disease of the central nervous system, characterized by highly variable and unpredictable course [12,13]. Concurrence of AIH and MS has rarely been reported in the past, either in untreated patients with MS, or after immunomodulatory treatment [14—16]. The prevalence of AIH in a large untreated population of MS patients was estimated 0.17% which is 10 times higher than that observed in the general population, suggesting common pathogenetic mechanisms between AIH and MS [10,17]. Additionally, a retrospective analysis of extrahepatic manifestations in 562 patients with AIH, found a 0.4% prevalence of MS [15]. Treatment-induced AIH has also been reported sporadically in patients with MS in conjunction with disease modifying agents, including the administration of interferon-beta (IFN-β)-1a, corticosteroids and copolymers (glatiramer acetate, COP-1) [16—20].

Herein, we report a large cohort of 14 patients with MS, who diagnosed with AIH during evaluation for deranged liver function tests. In most of them, the preceding immunomodulatory treatment with IFN-β and methylpredsnisolone pulses was considered the most likely precipitating factor for the development of AIH highlighting the difficulties in the diagnosis of AIH in patients with MS under immunosuppression but also underlining the importance of autoantibody serology and liver histology in establishing the diagnosis of AIH in such cases.

Table 1 Demographic, clinical and laboratory characteristics of the 14 patients with MS at the time of diagnosis.

Age (years)	36.7 ± 9.3
Sex (female/male)	13/1
Type of MS	
Relapsing remitting	12 (86%)
Progressive relapsing	1 (7%)
Clinical isolated syndrome	1 (7%)
ALT and or AST (ULN: 40 IU/L)	
< ULN	7 (50%)
> ULN	4 (29%)
Not available	3 (21%)
IgG (ULN: 1500 mg/dL)	
< ULN	2 (14%)
> ULN	2 (14%)
Not available	10 (72%)
Concurrent autoimmune diseases	4 (29%)

MS: multiple sclerosis; ALT: serum alanine aminotransferase; AST: serum aspartate aminotransferase; ULN: upper limit of normal. Autoantibodies had been evaluated in 4 patients (29%), 3 patients being positive for anti-nuclear antibodies (titers range: 1/80—1/320).

Patients and methods

From 2005 to 2017 we identified 14 patients with AIH from our entire prospective database of 184 patients with AIH who suffered from MS and had been referred to our department for assessment because of deranged liver function tests (Table 1). Diagnosis of MS was based on established criteria [12,13]. At the time of evaluation, 13 patients were under treatment for MS, while the remaining 1 patient had never received specific treatment. Actually, a variety of treatment regiments were reported during the course of MS up to the time of evaluation in our department. In more detail, 1 patient (8%) had received IFN-β monotherapy, 8 patients (61%) both IFN-β and steroids [5 (38%) were treated with high-dose methyprednisolone pulses and 3 (23%) with steroids orally] and 4 patients (31%) received monotherapy with high-dose methylprednisolone pulses. Considering IFN-β, this was the initial treatment regime in 3 patients, the ensuing regime in other 3 patients, while there was no information in the remaining 3 patients, who received combination treatment. Median duration of treatment with

IFN-β was 12 months (range: 1—312). Median duration of IFN-β treatment up to the first report of deranged liver function tests was 12 months (range: 1—120). All subjects gave written informed consent to participate in the study at the time of interview. The ethical committee of the University Hospital of Larissa approved the protocol, which conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Results

Before referral to our department, 7/14 (50%) patients had at least 1 episode of elevated aminotransferases in the past, which was attributed to IFN-β-related DILI in 2 of them. Among these 7 patients, 4 had undergone liver biopsy, while only 1 had available autoantibody testing. The diagnosis of AIH was established in only 1 of these patients, who received a course of prednisolone in combination with azathioprine for 1 year but relapsed after treatment withdrawal.

Upon referral to our department all patients were thoroughly investigated for the significant increase of aminotransferase levels (Table 2). In more detail, 11/14 patients (78.6%) had ALT levels > 10xupper limit of normal (ULN) while the remaining patients (21.4%) had ALT levels > 5x ULN. One of them (7.1%) developed jaundice, while none progressed to acute liver failure. Serological markers for acute hepatitis A, hepatitis B, hepatitis C and hepatitis E were negative for all patients, while alcohol misuse and other toxic and metabolic causes like Wilson's disease were appropriately ruled out. IgG serum levels were above the ULN in 6 (43%) and within the normal limits in 8 patients (57%), including 3 on combination treatment (IFN-β and steroids), 4 on recent methylprednisolone pulses and 1 untreated patient. Auto-antibody testing was performed in all patients as described previously [21—24]. In more detail, anti-nuclear (ANA), smooth muscle (SMA), liver/kidney microsomal type 1 (anti-LKM-1) and liver cytosol type 1 (anti-LC1) antibodies were detected by indirect immunofluorescence on 5-μm fresh-frozen sections of in-house rodent multi-organ (kidney, liver and stomach) tissue substrates [21—23]. Anti-LKM-1, anti-LC1 and antibodies against soluble liver antigens/liver pancreas (anti-SLA/LP) were also evaluated by Western immunoblot using rat liver microsomal or cytosolic extracts [21—24]. In addition, commercially available ELISA kits (INOVA, Diagnostics Inc., San Diego, CA, USA) using recombinant SLA/LP/tRNP(Ser)Sec were also used for anti-SLA/LP determination according to the manufacturer's instructions [24]. At the time of evaluation, all patients had at least 1 auto-antibody detected. In fact, 14 patients (100%) had detectable SMA, 5 (36%) had ANA, 3 (21%) had anti-SLA/LP, 2 (14%) had anti-LKM1 and 1 patient (7%) had anti-LC1 anti-bodies (Table 2).

A liver biopsy was performed in all patients at the time of evaluation. The results showed histological features compatible or typical with AIH, including interface hepatitis with dense plasma cell-rich lymphoplasmocytic infiltrates, hepatocellular rosette formation and emperipolesis in 11 (79%) and minimal and/or mild changes in 3 patients (21%). The histological activity index in the 11 patients according to the Ishak modified index [25] revealed moderate inflammatory activity in 8 and severe activity in 3 patients. In more detail, the activity index was 9.1 ± 3.9 (mean ± SD) for the total number of patients (n = 14) and 10.8 ± 2.2 for those with moderate and/or severe activity (n = 11). Of interest, 10/14 patients (71.4%) had centrilobular necro-inflammation and bridging necrosis while 2 (14%) had already features of cirrhosis.

Table 2 Demographic, clinical, laboratory and histological characteristics of the 14 patients with multiple sclerosis at the time of referral because of deranged liver function tests (elevated aminotransferases).

Age (years)	43.1 ± 12
ALT (IU/L, ULN: 40)	520 (115—1219)
AST (IU/L, ULN: 40)	278 (55—1121)
γ-GT (IU/L, ULN: 55)	95 (17—450)
Bilirubin total (mg/dL, ULN < 1.1)	1 (0.6—4.6)
INR	1.06 ± 0.5
IgG (mg/dL, ULN: 1500)	1367 (816—3580)
IgG > x ULN	6 (43%)
Detection of at least 1 auto-antibody	14 (100%)[a]
ANA	5 (36%)
SMA	14 (100%)
Anti-SLA/LP	3 (21%)
Anti-LKM-1	2 (14%)
Anti-LC1	1 (7%)
Serology compatible for acute HAV, HBV, HCV, HEV	0 (0%)
Histology	
Compatible/typical for AIH	11 (79%)[b]
Minimal changes	3 (21%)

Values are expressed as median (range) or mean ± standard deviation, unless otherwise stated. ALT: serum alanine aminotransferase; AST: serum aspartate aminotransferase; ULN: upper limit of normal; γ-GT: γ glutamyl transferase; INR: international normalized ratio; ANA: anti-nuclear antibodies; SMA: smooth muscle antibodies; anti-SLA/LP: soluble liver antigen/liver pancreas antibodies; anti-LKM-1: liver/kidney microsomal antibody type 1; anti-LC1: liver cytosol type 1 antibodies; HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus.

[a] Eight patients (57%) had 1 autoantibody detectable (SMA), 2 (14%) had 2 autoantibodies (ANA + SMA and SMA + anti-LKM-1, respectively), 3 (21%) had 3 autoantibodies (ANA + SMA + anti-SLA/LP in 2 and ANA + SMA + anti-LC1 in 1) and 1 patient (7%) had 4 autoantibodies (ANA + SMA + anti-SLA/LP + anti-LKM-1).

[b] Including 2 patients with already established cirrhosis.

A clinical diagnosis of AIH was made according to the descriptive criteria of the International AIH Group (IAIHG) published in 1999 [26], although the application of the simplified score for the diagnosis of AIH published by the same group in 2008 was compatible with definite AIH (Score 7) in 4 patients (29%) and probable AIH in 5 patients (36%) [27]. The interval between the diagnosis of MS and AIH diagnosis was 32 (2-312) months.

Treatment of AIH

Thirteen out of 14 patients with MS were treated for the underlying AIH as in the remaining patient the liver func-

tion tests normalized spontaneously, shortly after the liver biopsy and therefore, the patient refused treatment. Ten patients were treated with a combination of prednisolone plus mycophenolate mofetil (MMF) according to the protocol published recently by our group [22,24,28], whereas 3 patients were treated with conventional combination treatment of prednisolone plus azathioprine (AZA) as these 3 patients did not give written consent to participate in the MMF protocol. In both arms, prednisolone was instituted daily at one dose in the morning (0.5—1 mg/kg/day) according to the European Association for the Study of the Liver (EASL) and Hellenic Association for the Study of the Liver (HASL) clinical practice guidelines [10,11] followed by a gradual tapering (5 mg/week till the dose of 15 mg and then the tapering rate was 2.5 mg/week according to the biochemical and clinical response until complete withdrawal). MMF was started along with prednisolone if only bilirubin was less than 4 mg/dL at a dose of 1 g/day, divided in 2 doses and was then gradually increased in 3 weeks to a final dose of 1.5—2 g/day and maintained for at least 2 years after complete response (CR) according to our recent publications and EASL and HASL clinical practice guidelines [10,11,22,24,28]. AZA was added after 2 weeks of treatment with prednisolone and increased gradually to a final dose of 1—2 mg/kg/day [10,11,28]. According to our practice, after corticosteroid withdrawal and achievement of CR for at least 2 years, MMF was reduced to 1—1.5 g/day [11,22,23,28].

According to our recent publications and EASL and HASL clinical practice guidelines [10,11,22,24,28] CR was defined by the normalization of transaminases and IgG, improvement or disappearance of symptoms and liver histology, if performed, showing minimal or no inflammation. Partial response (PR) was defined by partial decrease of transaminases below 2xULN without achieving complete normalization and inability to withdraw or taper prednisolone. No response (NR) was defined by persistently elevated transaminases more than 3xULN and/or high IgG levels despite intensive immunosuppression and reassurance of compliance to therapy. Relapse was defined by the rise of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above 2—3xULN and/or elevation of IgG above 2000 mg/dL with or without reappearance of symptoms at any time-point during therapy following an initial CR.

Initial CR was achieved in all treated patients (13/13; 100%), as defined by statistically significant decrease in AST, ALT and IgG from the first month of treatment [10,11]. This initial CR was not associated with the kind of treatment that the patients had received for the management of MS prior to the diagnosis of AIH. At the time of this writing, 11/13 patients (85%) achieved maintenance of CR, including 9 (70%) after prednisolone withdrawal and 2 patients during the process of prednisolone tapering. The remaining 2/13 patients (15%) with initial CR suffered a relapse either during prednisolone tapering or after prednisolone withdrawal and therefore, prednisolone was either reinstituted or the dose was increased (Fig. 1).

According to the EASL and HASL guidelines [10,11], candidates for immunosuppression withdrawal are those who have been treated for at least 3 years and in conjunction had achieved continuous CR for at least the last 2 years of

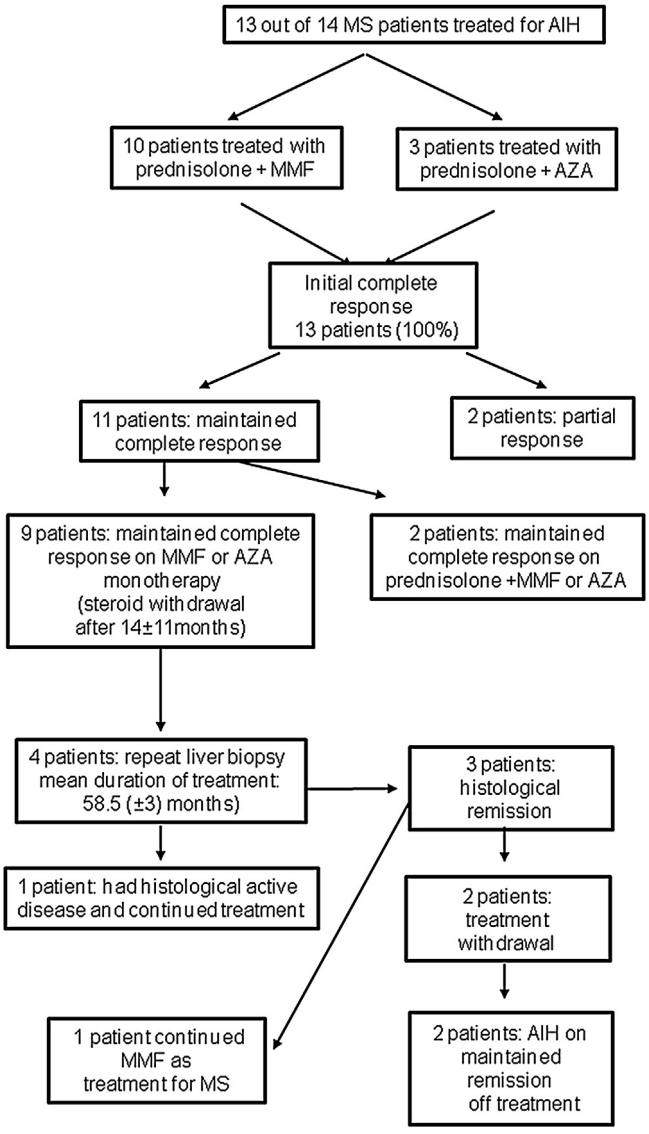

Fig. 1 Flowchart presentation of treatment and response to treatment at last follow-up in 13 patients with multiple sclerosis who diagnosed with autoimmune hepatitis and received treatment.

treatment. At the time of this writing 2 patients have fulfilled the above criteria and complete drug withdrawal was done. In more detail, 4/8 patients having maintained CR on MMF treatment for 59 ± 3 months, underwent a repeat liver biopsy. One patient demonstrated continued histological disease activity and as a consequence treatment was maintained while the rest 3 patients had histological remission (immunosuppression was withdrawn in 2 and continued in one as a result of a mutual decision between the patient and her neurologist in order to maintain remission of MS). In these 2 patients who stopped treatment, the off-treatment long-term remission is up to now 58 and 79 months respectively. The median time of follow-up since AIH diagnosis in the whole cohort of patients was 52.5 (range: 8—150) months (Fig. 1).

Treatment for MS after the diagnosis of AIH

After the diagnosis of AIH and during the follow-up period, 6 of 14 (43%) patients received in parallel with AIH treatment, specific treatments for MS exacerbation namely glatiramer plus methylprednisolone pulses, while 1 of them received also natalizumab without any new increase of aminotransferases in any of these 6 patients as all patients continued to receive either MMF or AZA with or without prdenisolone. Of note, pulsed therapy with methylprednisolone was not reintroduced in any of the 4 patients who developed AIH while being under pulsed methylprednisolone therapy alone.

Discussion

To the best of our knowledge, we report herein the largest case series of patients with MS, who developed AIH during the process of their underlying demyelinating disease. Of note, in the vast majority of patients (13/14; 92.9%), the development of AIH was associated with previous IFN-β and/or steroid treatment that had been applied for MS.

IFN-β is among the drugs approved for the treatment of relapsing remitting MS [29]. Type I IFNs have been broadly used in medicine due to their antiviral and immunomodulatory properties [30]. Specifically, IFNs are characterised by a pleiotropic action on the immune system and have been linked to the development of chronic inflammation and autoimmunity, through the prevention of both apoptosis of activated T cells and expansion of memory cells [30]. Along this line, IFNs have also been shown to activate autoreactive cells via stimulation of antigen presenting cells and enhancement of humoral immunity [31]. In patients with MS, treatment with IFN-β has been associated with an imbalance between anti-inflammatory and pro-inflammatory cytokines, while modulation of regulatory T (Treg) cell function and induction of naïve Treg populations has also been reported [32,33].

Most of patients with MS and especially those with the relapsing remitting form of the disease, often receive IFN-β in conjunction with mehylprednisolone pulses. For these reasons we cannot easily designate which of these drugs could be the principal triggering agent for the development of AIH. Although rare, the development of AIH has already been reported after the administration of high-dose intravenous methylprednisolone pulses in patients with autoimmune diseases including MS and Grave's ophthalmopathy potentially as a result of an immune rebound phenomenon after withdrawal of immunosuppression [34—38]. Therefore, we believe that a baseline assessment of LFTs before pulsed therapy with methylprednisolone but also after the end of therapy should be provided in all patients with MS who will receive this kind of treatment.

IFN-β has been associated frequently with adverse reactions, including induction of autoimmune phenomena and severe liver dysfunction, as has also been reported for IFN-α treatment for viral hepatitis [39—41]. Studies on IFN-β in patients with MS have reported increased probability of deranged liver function tests during treatment (up to 67% in a 24-month period), suggesting a causal relationship with the drug [42—44]. These changes considered to occur temporarily with rare need of treatment and therefore, have been thought of no major clinical significance in the majority of cases [42]. These studies underscored also the lack of correlation between liver dysfunction and the presence of organ and non-organ specific autoantibodies before or during treatment, suggesting that IFN-β is not associated with autoimmunity induction and can be considered safe [42,43]. Of note, the absence of symptoms, the preponderance of males and the abovementioned lack of association between autoantibodies and liver derangement in these patients have led to the assumption that induction of AIH by IFN-β is rather an unlikely event [44].

However, the absence of symptoms and the male sex should not exclude the diagnosis of AIH. AIH is a disease characterized by vast heterogeneity in terms of clinical presentation, biochemical, serological and histological features [1—3,10,11]. Therefore, it is not a surprise that the diagnosis of AIH can be mistakenly missed in a considerable proportion of patients either because of the fact that the disease does not manifest typically in terms of clinical and/or laboratory characteristics, or because of the lack of suspicion of AIH presence by the treating physician. Recognition of AIH as a cause of acute hepatitis is vital, bearing in mind that delay in immunosuppression initiation may result in liver failure and the need for liver transplantation [10,11,45]. Clinical suspicion and exclusion of other causes of liver diseases, including viral hepatitis, metabolic, toxic and genetic diseases are essential [1—3,10,11]. The characteristic phenotype of AIH consists of insidious or acute onset derangement of liver enzymes, mainly of hepatitic pattern, hypergammaglobulinemia, presence of organ and non-organ specific autoantibodies and characteristic histological changes [10,11].

In our cohort testing of IgG and autoantibodies at the time of MS diagnosis was performed in only 29% of patients while aminotransferase values were available in 11 out of 14, including 4 with increased aminotransferase levels. We cannot exclude the presence of AIH beforehand, considering scarcity of data in the majority of patients and no further assessment in those with deranged liver function tests.

Typically, patients with AIH are characterized by increased IgG serum levels. Of interest, the determination of IgG is frequently missing in every-day clinical practice during the evaluation of elevated liver function tests, which in turn may result in further underestimation of AIH diagnosis [2,3,10,11]. However, it is essential for physicians to keep in mind that IgG levels can be absolutely normal in a proportion of AIH patients as for instance in those with an acute-severe disease onset (25-39%) [2,10,11,45]. Indeed, more than half (57%) of our patients had normal IgG levels, probably because of the recent steroid treatment and the acute onset of the disease as attested by the findings on liver histology which were compatible with an acute form of AIH in the majority of them (71.4% of patients had centrilobular necro-inflammation and bridging necrosis at diagnosis).

Detection of non-organ and liver-related auto-antibodies remains fundamental for the diagnosis of AIH [2,3,10,11,23]. In order to avoid false negative results, it is of outmost importance to comply with the clinical practice guidelines [10,11,21,23], taking into accounting the appropriate methods that should be applied. For this reason it is sometimes essential to identify reference laboratories for

auto-antibody testing who have attained expertise in liver autoimmune serology [10,11].

In line with this, all of our patients had at least 1 autoantibody detected during evaluation in our department, including 5 patients (36%) with liver-specific autoantibodies (anti-SLA/LP, anti-LC1 or anti-LKM-1). Detection of liver-specific autoantibodies can assist the diagnosis of AIH in ANA and SMA negative cases that could be missed if only conventional autoantibodies had been tested as part of the evaluation of elevated aminotrasferases in patients with clinical suspicion of AIH [2,3,10,11,21,23].

Liver histology remains a prerequisite for the diagnosis of AIH, since transaminases and IgG levels do not always correspond either to the inflammatory activity or the stage of fibrosis [10,11]. The application of non-invasive methods has serious limitations especially in cases of acute hepatitis due to interference of liver inflammation with the measurement of liver stiffness [46]. Typical histological features of the chronic form of AIH, though not specific, are the presence of interface hepatitis, hepatocytes rosetting and emperipolesis [2,3,10,11]. However, in patients presenting with the acute form of the disease, panacinar hepatitis (parenchymal collapse) and perivenular necroinflammation (including centrilobular necrosis) as found in the majority of our patients, may predominate, resembling mostly DILI or toxic injury [10,11,45,47]. Additionally, presence of portal lymphoid follicles, plasma cell-rich inflammatory infiltrate and central perivenulitis have been suggestive of AIH-related acute liver failure [45,47]. In the present study, 11 out of 14 patients had typical histological features for AIH including 10 with characteristic features of acute disease onset [45,47]. The rest 3 patients had minimal and/or mild changes, which could be attributed to the previous corticosteroid administration for the management of MS. Of note, 2 patients had already histological features of established cirrhosis, implying this episode as an acute-on-chronic episode of chronic AIH that has been previously misdiagnosed and/or underdiagnosed [2,3,10,11,45,48]. The chronic nature of AIH in some of our patients is further supported by the fact that half of our patients had at least 1 episode of increased aminotransferases in the past that was attributed to IFN-β associated DILI in 2 of them, while the diagnosis of AIH was established in only 1 patient.

Indeed DILI often shares common features with AIH, particularly at the histological level. In this context, a recent study has suggested a combination of histological findings that could be used in order to discriminate DILI versus AIH [49]. In our large cohort the histological features pointed towards the diagnosis of AIH in the majority of patients, even though most of them were under corticosteroid treatment which is well known that affects several distinct histological findings of AIH.

Another issue that has gained special interest is the use of scores as diagnostic tools for the diagnosis of AIH. Along this line, a simplified score has been proposed that combines the presence and titer of autoantibodies, serum IgG levels, the presence of typical or compatible histological features and the absence of viral hepatitis markers [27]. In atypical cases, including the acute onset of AIH or the AIH-related variant syndromes, this score does not work effectively as some of the characteristic features of AIH might be missing [10,11,45,47]. Indeed, 5 of the 14 patients included in our study had simplified scores that did not correspond to possible or definite AIH diagnosis and this, as already stated, most probably was due to the normal IgG levels in 57% of patients and minimal and/or mild changes in liver histology in 21%. In summary, our data support previous studies which have shown that scoring systems must be used with caution and always alongside right clinical judgment [10,11,50].

Treatment of AIH is of outmost importance, especially in patients with clinical, biochemical and histological active disease, since it has been associated with histological remission and improved survival [1—3,10,11]. The vast majority (85%) of our treated patients achieved complete on-treatment response. Amongst them, 4 patients underwent a second liver biopsy after having completed a mean duration of treatment with MMF of 59 months, which showed histological remission in 3 and led to treatment discontinuation. Up to the time of this writing, 2 of these patients remain in off-treatment response for more than 4 years.

Of note, 10 of 13 patients were treated with MMF and prednisolone combination, as part of a prospective observational trial conducted in our department assessing MMF as first line treatment for AIH [21,28,51]. In this study, acute presentation was an independent predictor of CR to treatment, as was also the case in our cohort of patients with MS and AIH [28].

In conclusion, AIH and MS are both relatively rare autoimmune diseases associated with dysregulation of the immune system. MS treatment with immunomodulatory agents, including IFN-β and high-dose methylprednisolone pulses might alter immune responses to liver antigens and along this line trigger or unmask latent AIH. Accordingly, the differential diagnosis of hepatitis in patients with MS should include AIH and particularly when the patients are under immunomodulatory treatment for MS. Hence, it is mandatory to further assess deranged liver function tests in conjunction with the drug history that might alter the typical disease phenotype. Mandatory tools for further evaluation of these patients should be the liver autoimmune serology performed ideally in reference laboratories in addition to liver histology. Prompt diagnosis and treatment of AIH in patients with MS is essential, safe and efficient for induction of disease remission as complete or partial response was recorded in all of our patients.

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Disclosure of interest

The authors declare that they have no competing interest.

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