International Archives of Medical Research 16:2 (2024) 13-23

ORIGINAL RESEARCH

General Characteristics of Our Patients Diagnosed with Autoimmune Hepatitis: Single Center Experience

Received Date: 26.03.2024, Accepted Date: 05.06.2024 **DOI: 10.56484/iamr.1454580**

Ramazan YOLAÇAN[1a*], Cihat YILDIRIM[2b], Muhsin KAYA[3c]

[1] [1]Bingöl State Hospital, Department of Gastroenterology, Bingöl, Türkiye;
[2]Dr. Yusuf AZİZOĞLU Silvan State Hospital, İnternal Medicine Diyarbakır, Türkiye;
[3]Dicle University, Faculty of Medicine, Department of Gastroenterology, Diyarbakır, Türkiye;
[a]*ORCİD: 0000-0002-9427-5341,* [b]*ORCİD: 0000-0002-7324-3578,* [c]*ORCİD: 0000-0002-7178-360X*

Abstract

Objective: *Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease of unknown etiology. Our aim was to investigate the general characteristics of our AIH patients, the treatments administered, and the responses to these treatments, and to compare these with the data available in the literature.*

Method: *Between 2010-2020, data from 62 patients diagnosed with AIH at our clinic were retrospectively reviewed. The study investigated the general characteristics at the time of diagnosis, laboratory values, autoantibody levels, liver histology, treatment status and responses, as well as follow-up and survival times.*

Results: *Of the patients, 57 were female, the average age of was 34.76±14.9 years. At the time of diagnosis, a more than tenfold increase in aminotransferase levels and acute hepatitis were statistically significantly higher in females($p<0.05$). While there was a statistically significant relationship between the average time to remission and aminotransferase levels($p<0.05$), no significant relationship was found between the development of relapse($p>0.05$).*

Conclusion: *AIH should always be considered in patients with acute and chronic liver disease, hypergammaglobulinemia, and especially those with other autoimmune diseases. It is important to remember that AIH responds well to treatment and patients can be maintained in remission for extended periods with appropriate therapy.*

Keywords*: ANA, Autoimmune hepatitis, Cirrhosis*

Introduction

Autoimmune hepatitis (AIH) is a chronic progressive inflammatory liver disease that arises due to the loss of self-tolerance against liver antigens. Its etiology is not fully understood, and it can occur across all ethnic groups and ages. Like most autoimmune diseases, AIH is more commonly seen in females. AIH is divided into two types based on the accompanying autoantibodies. Type 1 AIH is

Corresponding author: E-mail: dryolacan@gmail.com.tr

more common in children and adults, while Type 2 AIH is more often observed in children and adolescents. The incidence and prevalence of the disease worldwide are 0.7-2/100,000 and 4-25/100,000, respectively [1,2]. Although the exact etiology of AIH is unknown, genetics, age, gender, and environmental factors are suggested to play a role in its development. The heterogeneity in clinical presentation can complicate the diagnosis of the disease. Patients may present with symptoms ranging from asymptomatic transaminase elevation to acute, fulminant, chronic hepatitis, and signs of liver cirrhosis [3].

The diagnosis of AIH is made using the scoring system developed by the International Autoimmune Hepatitis Group (IAHG) in 1993 and revised in 1999. This system includes numerous parameters such as gender, autoantibodies, immunoglobulin G (IgG) and liver enzyme levels, alcohol consumption, exposure to hepatitis viruses and hepatotoxic agents, the presence of concomitant autoimmune diseases, histopathological findings, and the response to treatment [4]. All viral hepatitides, especially those caused by hepatitis viruses, toxic hepatitis, and drug-related hepatitis should be considered in the differential diagnosis of AIH [5].

Immunosuppressive therapies administered halt the progression of the disease, lead to a regression in fibrosis score, and prevent the progression to cirrhosis. Therefore, suspecting the disease and making an early diagnosis is very important [6]. The initial treatment is planned according to the patient's age, comorbid conditions, and disease activity. In the initial treatment, corticosteroids are given alone or in combination with azathioprine. Alternative immunosuppressive agents such as mycophenolate mofetil, tacrolimus, cyclosporine, sirolimus, and budesonide are used for patients who do not respond to conventional treatments or to minimize the side effects associated with corticosteroids [7]. Mycophenolate mofetil is the first choice among alternative agents. The goal of the treatment is to achieve sustained remission without medication. Liver transplantation can be performed for patients who develop acute liver failure, decompensated cirrhosis, and hepatocellular carcinoma [8].

Materials and Methods

At the Internal Medicine and Pediatrics clinics of Dicle University Faculty of Medicine, 62 patients diagnosed with autoimmune hepatitis between 2010-2020 and whose data were accessible were included in the study. Patients with malignancy, active infection, chronic haematological disease and pregnant women were excluded. Data regarding the patients gender, age at initial diagnosis, exposure to drugs, alcohol, and toxic substances, as well as the history of autoimmune diseases in the patients themselves and their close relatives were recorded. During the initial diagnosis and

subsequent follow-ups, laboratory data such as complete blood count, ALT, AST, ALP, GGT, total bilirubin, albumin, and IgG levels were examined. The titers of autoantibodies and viral markers (HBsAg, anti-HBs, anti-HCV, anti-HAV IgM) checked at the initial diagnosis were recorded. Histological data from liver biopsies, including findings such as interface hepatitis, lymphoplasmacytic cell infiltration, rosette formation, bile duct changes, and the presence of granulomas, were investigated. Findings compatible with cirrhosis in ultrasound and/or tomography examinations at the initial diagnosis were recorded. The patients' disease status at hospital admission (acute hepatitis, chronic hepatitis, acute liver failure, and cirrhosis), the start date of treatment, medications and dosages used in treatment, complications developed during treatment, responses to treatment, and their latest status were documented. Patients with ALT and/or AST levels more than ten times the normal at initial diagnosis, without a history of chronic liver disease, and without cirrhosis findings in imaging were considered to have acute hepatitis. Those with clinical and/or imaging findings compatible with cirrhosis were considered to have cirrhosis. A complete response was defined as a return to normal levels of serum ALT and AST along with IgG after treatment, while those who did not drop below 50% of the normal levels during treatment were considered non-responsive. Those who showed more than a 25% increase in ALT, AST, and/or IgG levels after a complete response were considered to have relapsed.

The diagnosis of AIH was made using the scoring system developed by the International Autoimmune Hepatitis Group (IAHG) in 1999. According to the scoring system, those who scored 15 or above before treatment were considered definite AIH patients, and those who scored between 10 and 15 were considered probable AIH patients. After treatment, those who scored 17 or above were considered definite AIH patients, and those who scored between 12 and 17 were considered probable AIH patients.

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine with decision number 84 dated 05.03.2020.

Statistical Analysis

The statistical analyses of the results obtained in the study were performed using the SPSS (Statistical Package for the Social Sciences) 18.0 statistical software package. Descriptive statistics for continuous variables were expressed as mean ± standard deviation, minimum, and maximum values, while categorical variables were expressed as number and percentage. Additionally, the Chi-square test was used for the analysis of categorical variables. Overall survival, intra-group survival, and 5-year life expectancy were examined using the Kaplan-Meier test. In these tests, a p (probability) value of less than 0.05 was considered statistically significant.

Results

Of the 62 patients included in the study, 57 (91.9%) were female, with a female to male ratio of 11:1. The average age of the patients was determined to be 34.76±14.9 years (female 35±14.5 / male 32±21). The average follow-up period was 34.7±23.4 (1-60 months) months, during which 2 (3.2%) patients died. The average survival time of our patients was 105 months (standard deviation: 2.1; CI:101.5-110), and the 5-year survival rate was found to be 92%. The laboratory findings at the time of diagnosis are shown in Table 1. A viral hepatitis panel was examined in all patients, and HBsAg, anti-HCV, and anti-HAV IgM were found to be negative. None of the patients had a history of alcohol, drug, or toxic substance intake. Anti-HBs was positive in 29 patients (46.7%). At the initial diagnosis, acute hepatitis was present in 34 patients (54.8%), 33 of whom were female, and cirrhosis was present in 19 patients (30.6%). Acute hepatitis was significantly higher in females compared to males ($p<0.05$).

Table 1: Laboratory values of patients at the time of diagnosis

	Min.	Max.	Average	Reference
ALT(U/L)	48	2740	545,1	0-30
AST(U/L)	31	4202	535	0-30
ALP(U/L)	67	845	207	<150
GGT(U/L)	10	1482	199,9	<55
T.bil(mg/dl)	0,3	16,7	2,86	0,3-1,2
D.bil(mg/dl)	0,1	10,3	1,79	0-0,5
Globulin(g/dl)	3,2	8,4	4,88	2-3
IgG (mg/dl)	1160	5070	2261	<1600

AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, ALP: Alkaline Phosphatase, GGT: Gamma Glutamyl Peptidase, IgG: Immunoglobulin G

The number of patients with an increase in ALT and/or AST values more than tenfold at the time of diagnosis was 34 (54.8%) (33 females and 1 male). The increase in aminotransferase levels more than tenfold at the time of diagnosis was statistically significantly higher in females ($p<0.05$). Of the 43 patients who were treated and followed up after treatment, 25 (58.1%) (24 females and 1 male) had aminotransferase levels increased more than tenfold. While the average time to remission for these patients was 13 months, the average time to remission for patients with less than a tenfold increase in aminotransferase levels was 9.3 months. The average time to remission for patients, regardless of aminotransferase levels, was found to be 11 months. There was a statistically significant relationship between the average time to remission and aminotransferase levels ($p<0.05$). Of the 19 patients who relapsed, 10 (52.6%) had an increase in aminotransferase levels more than tenfold at the initial diagnosis. No statistically significant relationship was found between the aminotransferase levels at the initial diagnosis and the development of relapse ($p>0.05$). Of the 34

patients who showed more than a tenfold increase in liver enzymes at the time of diagnosis, 8 (23.5%) developed liver cirrhosis, while 24 (70.5%) did not have cirrhosis, and data for 2 patients were not accessible. No significant relationship was found between the increase in liver enzyme levels at the time of diagnosis and the development of liver cirrhosis ($p>0.05$).

The positivity rates of autoantibodies in our study were identified as follows: ANA (71.6%), ASMA (16%), anti-LKM1 (2%), AMA (15%), anti-LC-1 (5.1%), anti-SLA/LP (8.4%), and p-ANCA (20.8%). Among the patients included in the study, 38 (61.2%) had type 1 AIH, 3 (5%) had type 2 AIH, and 8 (12.8%) had overlap syndrome. Coexistence of AIH with primary biliary cholangitis (PBC) was found in 7 patients (11.2%), AIH with primary sclerosing cholangitis in 1 patient (1.6%), and seronegative AIH in 13 patients (21%). Additional autoimmune diseases were present in 23 patients (37.1%), with autoimmune thyroiditis (AIT) being the most common, observed in 10 patients (16.1%). PBC was seen in 7 patients (11.2%), SLE in 3 patients (4.8%), and RA in 3 patients (4.8%). No statistically significant relationship was found between liver enzyme elevation, the presence of additional autoimmune diseases, and autoantibody positivity ($p>0.05$).

Liver biopsies performed on patients showed interface hepatitis in all (100%), lymphoplasmacytic cell infiltration in 25 (59.5%), rosette formation in 12 (19.4%), and bile duct changes in 14 (22.6%). Interface hepatitis, lymphoplasmacytic cell infiltration, and rosette formation were present in 7 patients (11.3%), interface hepatitis and lymphoplasmacytic cell infiltration in 25 (40.3%), and interface hepatitis and rosette formation in 12 (19.4%). Histopathologically, interface hepatitis followed by lymphoplasmacytic cell infiltration was most frequently observed in patients who had more than a tenfold increase in liver enzymes at the initial diagnosis. However, no statistically significant relationship was found between enzyme elevation and any histopathological findings ($p>0.05$).

According to the IAHG scoring system, before treatment, 45 patients (72.5%) in our study had a definite diagnosis, and 17 (27.5%) had a probable diagnosis. The average IAHG score of the 43 patients treated and followed up before treatment was 17.44 (±2.7), while after treatment it was 19.9 (±3.7). The increase in the IAHG score after treatment was found to be statistically significant ($p<0.05$). Of the 43 patients treated and followed up, 35 (81.3%) had a definite diagnosis and 8 (18.7%) had a probable diagnosis at the time of diagnosis, while after treatment, 5 patients with a definite diagnosis shifted to the probable diagnosis category, and 4 patients with a probable diagnosis shifted to the definite diagnosis category. This necessitates scoring before and after treatment, as a statistically significant conversion was observed between patients with definite and probable diagnoses before and after treatment ($p<0.05$).

Azathioprine and prednisolone treatment were administered to 39 patients (62.9%), while only prednisolone treatment was given to 5 patients (8.1%). Information about the treatment of 18 patients (29%) could not be obtained. Of the 43 patients treated and followed up during the first 60 months, 26 (60.47%) responded completely to the treatment, 13 (30.23%) partially, and 4 (9.3%) did not respond. Azathioprine and prednisolone were given to 22 (84.6%) of the patients who achieved a complete response, while only prednisolone was given to 4 (15.4%). Relapse was observed in 19 (73%) of the 26 patients who achieved a complete response. On average, relapse occurred 19.77 months after remission. Decreases in liver enzyme, bilirubin, and IgG levels were observed from the first month of treatment. Significant reductions in ALT, AST, and IgG were detected at the end of the first month, while a significant reduction in total bilirubin was detected at the end of the third month ($p<0.05$). The decrease in ALP and GGT levels was not found to be statistically significant in relation to the treatment ($p>0.05$) (Figures 1,2,3).

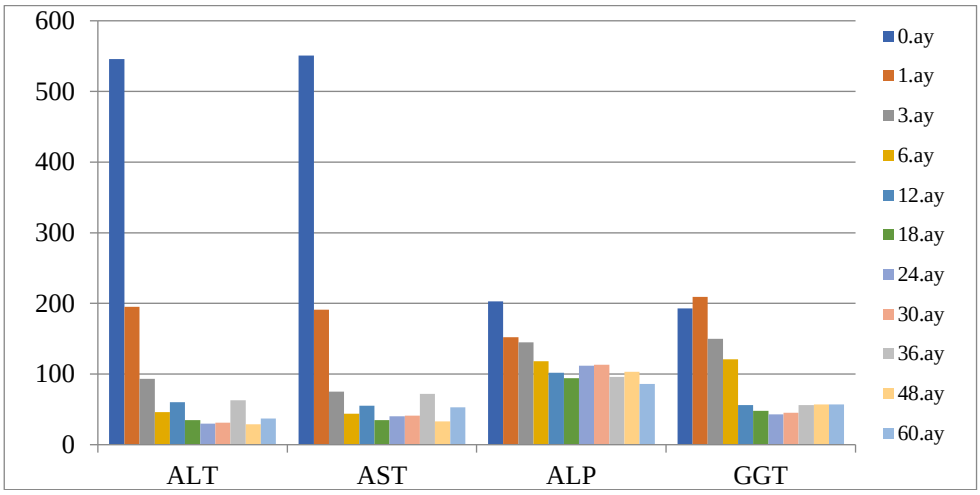

Figure 1: Monitoring of Biochemical Markers

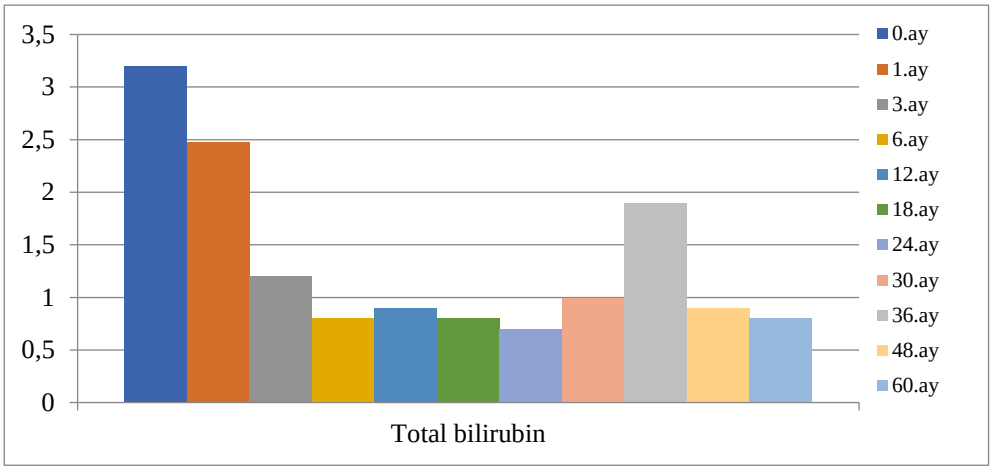

Figure 1: Total Bilirubin Monitoring

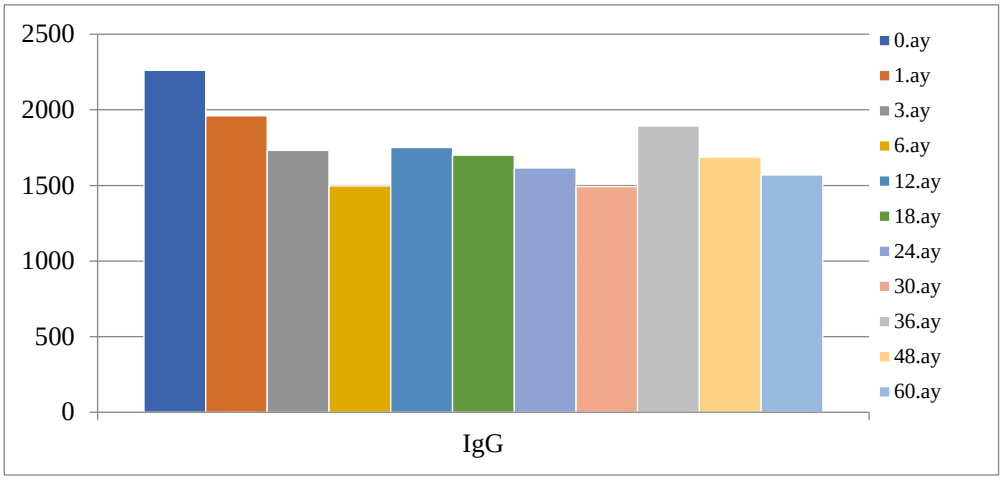

Figure 3: IgG Monitoring

Discussion:

Although the literature classically mentions a bimodal distribution of the peak age of patients with AIH in childhood and adulthood, recent studies emphasize that the disease can be seen at any age [9]. In a prospective study by Agarwal et al. in India, the age range of patients was taken as 5-61, with an average age of 31±17.1 [10]. Our study, similar to this one in terms of age range, also found a comparable average age (34.76 ± 14.9). As seen in our study, it has been reported by different authors that the majority of AIH patients are women [11]. In studies the F/M ratio is up to 6/1 [12]. In our study, the F/M ratio was determined to be 11.4/1, which is high compared to the literature, but the higher proportion of women is consistent with the literature. These data also show us that different ratios may exist in each region and race.

Studies conducted on different societies report that type 1 AIH is commonly seen in the adult population, constituting approximately 67-80% of cases [13]. In our study, type 1 AIH was found at a rate of 61.2%, which is slightly lower than the literature. The higher proportion of seronegative AIH cases in our study (21%) compared to the literature might be the reason for the lower rate of type 1 AIH cases found in our study. Type 2 AIH is seen much less frequently, constituting less than 10-15% of AIH cases in studies conducted in Europe and North America [14]. In our study, the rate of type 2 AIH was found to be below 10%. The rate of patients with overlap syndrome in our study was observed to be 12.8%. The coexistence of AIH with Primary Biliary Cholangitis (PBC) was 11.2% and with Primary Sclerosing Cholangitis (PSC) was 1.6%. Previously reported AIH-PBC ratios in the literature range from 2-20% [15]. The frequency of AIH-PSC overlap varies according to

diagnostic criteria and the population studied, and a recent review by Nayagam et al. reported a frequency ranging from 1.7-12.5% [16]. In a report by the Mayo Clinic, 162 type 1 AIH, 37 PBC, and 26 PSC patients, a total of 225 patients defined by standard criteria, were examined, and it was indicated that 18% of the patients showed features of overlap syndrome [17]. When we look at the literature, the rate of overlap syndrome varies even within the same societies.

The issue has been attributed to the use of different scoring systems and the lack of a standard diagnostic method [18]. In a large patient series evaluated by Czaja, ANA positivity in AIH was found to be 80%, while ASMA positivity was 63% [19]. In our study, while the ANA positivity rate (71.6%) was close to the literature, the ASMA positivity rate was found to be lower (16%) than the literature. In our study, p-ANCA positivity was observed in 8 of the 28 type 1 AIH patients (28.5%) for whom p-ANCA data were available. The literature has identified p-ANCA positivity in some patients with type 1 AIH [20]. In this respect, our study's data are consistent with the literature. In a study conducted by Abe et al., SLA/LP autoantibody positivity, specific to the disease, was detected in approximately 30% of patients diagnosed with AIH [21]. In our study, this rate was observed to be 8.4%, which is lower than the literature. In our study, AMA positivity was detected at a rate of 15%, which is consistent with the literature.

IgG levels may not increase in every case of AIH; indeed, in our study, IgG levels were found to be <2000 mg/dl in 27 of the 52 patients (51%) for whom data were available. In a large series study by Zeniya et al., serum IgG levels were found to be below 2000 mg/dl in 392 of 1008 patients (38.9%) [21]. Most patients in our study indicate that IgG levels can be normal at diagnosis. It is a known fact that there is an increase in the frequency of extrahepatic autoimmune diseases in AIH, and this has been reported to be between 20-50% in clinical studies [22]. Another autoimmune disease was present in 37.1% of the AIH patients in our study, which is similar to the literature. When we looked at the accompanying autoimmune diseases in our patients, AIT was most found to accompany (16%). In large series of recent reports, AIT has been reported to be the most common autoimmune disease accompanying AIH, similar to our study (7.5-18%) [23]. The presence of SLE was detected at 4.8% in our patients. In a study conducted by Mashiba et al., the coexistence of AIH with SLE was 3.1%, which is close to our study [21]. Another finding of our study is that the presence of extrahepatic autoimmune diseases is more common in female patients. It is already known that autoimmune diseases are more common in women. Therefore, it is not surprising that this pattern is also seen in AIH. As in many studies, Fabbri's study reported that the rate of accompanying autoimmune diseases was also higher in women with AIH [24].

In some studies, in the literature, a high rate of cirrhosis at the time of diagnosis, such as 33.9%, has been reported in patients diagnosed with AIH [25]. In a study conducted by Al Chalabi et al. in 2006, cirrhosis was detected at the time of diagnosis in 30% of patients with AIH, and some patients were observed to have complications of portal hypertension such as hypersplenism, esophageal variceal bleeding, and signs of decompensated liver disease [26]. Our cirrhosis rate at the time of diagnosis (30.6%) is consistent with the literature in light of this information. Interface hepatitis is a histopathological finding that strongly supports the diagnosis of AIH but can also be observed in hepatitis caused by other reasons. In a study conducted by Mulder et al. in 2016, interface hepatitis was reported in 84-98% of AIH cases [27]. The reason we observed interface hepatitis in all our patients is thought to be due to the high sensitivity of the pathology and our acceptance of a positive result even when the interface hepatitis score is ≥1, meaning that it is present even at a minimal-mild level.

Although different remission durations have been reported in the literature, the average time for patients to enter remission is stated to be 12 months [28]. The reason for this variability in the literature could be due to the different treatment regimens used. Studies have reported that 50-86% of patients develop relapse within one year after treatment cessation, necessitating the resumption of treatment, and relapse is often observed within the first 6 to 12 months [29]. While the relapse rates in our study (73%) are consistent with the literature, the time to relapse (19.77 months) was later. In a study conducted in South Korea, the mortality rate of the disease was found to be 2.18% [30]. In our study the mortality rate was 3.2%.

Due to the insufficient treatment follow-up data, we lack information on whether the treatment was stopped or not, how long the patient received treatment, and if they entered remission, how much longer they were followed up with treatment or without treatment. Also, for some patients whose treatment status is unknown, although they had laboratory follow-ups after diagnosis, follow-ups related to treatment could not be performed.

Another area of limitation was related to the definition of remission. In our study, the definition of remission was based on biochemical values, and the histological remission criterion could not be used due to the absence of control biopsies or, more precisely, the lack of data on this matter. This is because some guidelines consider histological improvement as a criterion for ideal remission [31]. On the other hand, the British Society of Gastroenterology suggests that treatment can be terminated if liver enzyme and immunoglobulin levels remain normal for a certain period after treatment [32].

Conclusion

In our study, we believe that AIH plays a significant role in the etiology of acute and chronic liver diseases observed in our region, and especially in patients with elevated liver enzymes and increased IgG levels, without a history of viral marker positivity, alcohol, toxic substance, drug use, and with positive autoantibodies, AIH must be considered. When starting treatment in these patients, the current clinical picture of the patient, the response to medications, and drug complications should be taken into account. It should not be forgotten that these patients need to be followed up regularly and for an extended period.

Conflict of interest: The authors have no conflict of interest related to this study.

Financial Support: No financial support was received for this study.

References

1. Ngu JH, Bechly K, Chapman BA, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol 2010;25:1681-6.

2. Delgado JS, Vodonos A, Malnick S, et al. Autoimmune hepatitis in southern Israel: a 15-year multicenter study. J Dig Dis 2013;14:611-8.

3. EASL Clinical Practice Guidelines: Autoimmune hepatitits, journal of hepatology 2015 volume 63, 971-1004.

4. Lohse AW, Vergani GM. Autoimmune hepatitis, journal of hepatology 2011 volume 55, 171-182.

5. Gatselis NK, Zachou K, Koukoulis GK, Dalekos GN. Autoimmune hepatitis, one disease with many faces: Etiopathogenetic, clinico-laboratory and histological characteristics, World J. Gastroenterology 2015 January 7; 21 (1): 60-83.

6. Manns PM, Lohse AW, Vergani D. Autoimmune hepatitis–Update 2015, journal of Hepatology 2015 volume 62, 100–111.

7. Rizvi S, Gawrieh S. Autoimmune Hepatitis in the Elderly: Diagnosis and Pharmacologic Management, Springer International Publishing AG, 4 July 2018, 589-602.

8. Gleeson D, Heneghan MA. British Society of Gastroenterology. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011; 60, 1611-1629.

9. Manns MP, Vergani D. Autoimmune hepatitis. Semin Liver Dis. 2009; 29 (3): 239-240.

10. Gupta R, Agarwal SR, Jain M, et al. Autoimmune hepatitis in the Indian subcontinent: 7 years experience. J. Gastroenterology Hepatology 2001; 16 (10): 1144-1148.

11. Peng M, Li Y, Zhang M, et al. Clinical features in different age groups of patients with autoimmune hepatitis. Exp. Ther. Med. 2014; 7 (1): 145-148.

12. Van Gerven NM, Verwer BJ, Witte BI, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J. Gastroenterology 2014 Oct; 49 (10): 1245-1254.

13. Czaja AJ, Manns MP. The validity and importance of subtypes in autoimmune hepatitis: a point of view. Am. J. Gastroenterology 1995; 90 (8): 1206-1211.

14. Granito A, Muratori L, Pappas G, et al. Clinical features of type 1 autoimmune hepatitis in elderly Italian patients. Aliment Pharmacol Ther 2005 Sep; 21: 1273-1277.
15. Czaja AJ. The overlap syndromes of autoimmune hepatitis. Dig. Dis. Sci. 2013; 58 (2): 326-343.
16. Nayagam JS, Miquel R, Joshi D. Overlap Syndrome with Autoimmune Hepatitis and Primary Sclerosing Cholangitis EMJ Hepatology 2019; 7 (1): 95-104.
17. Liberal R, Grant CR, Mieli-Vergani G, et al. Autoimmune hepatitis: A comprehensive review. Journal of Autoimmunity. 2013; 41: 126–139.
18. Chazouilleres O. Diagnosis of primary sclerosing cholangitis autoimmune hepatitis overlap syndrome: to score or not to score? J. Hepatology 2000; 33 (4): 661-663.
19. Czaja AJ. Performance parameters of the conventional serological markers for autoimmune hepatitis. Dig. Dis. Sci. 2011; 56 (2): 545-554.
20. Mieli-Vergani G, Heller S, Jara P, et al. Autoimmune hepatitis. J. Pediatr. Gastroenterology Nutr. 2009; 49 (2): 158-164.
21. Abe M, Mashiba T, Zeniya M, et al. Autoimmune Hepatitis Study Group-Subgroup of the Intractable Hepato-Biliary Disease Study Group in Japan. Present status of autoimmune hepatitis in Japan: a nationwide survey. J. Gastroenterology 2011 Sep; 46 (9): 1136-1141.
22. Kil JS, Lee JH, Han AR, et al. Long-term treatment outcomes for autoimmune hepatitis in Korea. J. Korean Med. Sci. 2010; 25 (1): 54-60.
23. Takahashi A, Arinaga-Hino T, Ohira H, et al. Autoimmune hepatitis in Japan: trends in a nationwide survey. J. Gastroenterology 2017; 52 (5): 631-640.
24. Muratori P, Fabbri A, Lalanne C, et al. Autoimmune liver disease and concomitant extrahepatic autoimmune disease. Eur. J. Gastroenterology Hepatology 2015; 27 (10): 1175-1179.
25. Feld JJ, Dinh H, Arenovich T, et al. Autoimmune hepatitis: effect of symptoms and cirrhosis on natural history and outcome. Hepatology 2005; 42 (1): 53-62.
26. Czaja AJ. Global Disparities and Their Implications in the Occurrence and Outcome of Autoimmune Hepatitis, Dig. Dis. Sci. 2017 Sep; 62 (9): 2277-2292.
27. Van Gerven NM, De Boer YS, Mulder CJ, et al. Autoimmune hepatitis. World J. Gastroenterology 2016 May 21; 22 (19): 4651-4561.
28. Kil JS, Lee JH, Han AR, et al. Long-term treatment outcomes for autoimmune hepatitis in Korea. J. Korean Med. Sci. 2010; 25 (1): 54-60.
29. Czaja AJ, Carpenter HA. Histological features associated with relapse after corticosteroid withdrawal in type 1 autoimmune hepatitis. Liver international: official 113 journal of the International Association for the Study of the Liver. 2003; 23 (2): 116-123.
30. Yoshizawa K, Joshita S, Matsumoto A, et al. Incidence and prevalenceof autoimmune hepatitis in the Ueda area, Japan. Hepatol Dec. 2016;46(9):878-83.
31. Kil JS, Lee JH, Han AR, et al. Long-term treatment outcomes for autoimmune hepatitis in Korea. J. Korean Med. Sci. 2010; 25 (1): 54-60.
32. European Association for the Study of the (EASL) Clinical Practice Guidelines: Autoimmune hepatitis. J. Hepatology 2015; 63 (4): 971-1004.