

Review Article:

Simultaneous Presentation of Autoimmune Hepatitis and Wilson Disease: A Systematic Review Study



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ABSTRACT

Background: The specialists should identify the features of Wilson disease and autoimmune hepatitis when both affect a patient to adopt appropriate treatment.

Objectives: This study was conducted to determine features of the patient, disease, diagnostic studies, and therapeutic measures in cases of simultaneity of Wilson disease and autoimmune hepatitis.

Methods: To find evidence related to the study objectives, we searched databases such as Barakat knowledge network system, SID, Magiran, Google Scholar, Web of Science, ProQuest, Springer, ScienceDirect, Medline via PubMed, and Scopus with specified Persian and English keywords, including "Wilson's Disease", "Autoimmune", and "Hepatitis". The inclusion criteria for the studies were 1) the study was observational and 2) the study was published in Persian or English. The exclusion criteria included low-quality studies based on the score obtained from the checklist. The obtained studies were screened in terms of titles, abstracts, and full text, and finally, the qualified studies entered the review process. The relevant data were extracted according to a designed checklist.

Results: Finally, 10 studies were included in the review process. Information about 14 patients was reported. The Mean±SD age of the participants in the studies was 19±11 years. The direction of diagnosis was from autoimmune hepatitis to Wilson disease in 8 cases and from Wilson disease to autoimmune hepatitis in 3 cases. The simultaneity of autoimmune hepatitis and Wilson disease was considered in 3 patients with no primary and secondary diagnosis.

Conclusions: The comorbidity of Wilson disease and autoimmune hepatitis is uncommon but is important. In the presence of relevant symptoms in these patients, the comorbidity of these two diseases should be considered. Accordingly, additional assessments such as serum ceruloplasmin, urinary 24-h copper, molecular genetic testing, MRI, serological tests, anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, complement level, gamma globulin, IgG, albumin, Kayser-Fleischer ring eye examination, and liver biopsy should be considered for correct diagnosis. If appropriate treatment was started for the disease with a diagnosis of Wilson disease or autoimmune hepatitis, but the response to treatment was insufficient, it is better to consider the simultaneous occurrence of two diseases or the initial misdiagnosis.

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1. Introduction

Autoimmune hepatitis is a chronic inflammatory disease of unknown etiology characterized by circulating antibodies, hypergammaglobulinemia, inflammatory changes in necrotic liver tissue, and a significant response to immunosuppressive therapy [1]. The pathogenesis, diagnosis, and treatment of autoimmune hepatitis continue to challenge physicians [2] because the disease has a variety of clinical phenotypes, and this diversity complicates its diagnosis and management [3]. Autoimmune hepatitis, in most cases, responds to immunosuppressive therapy, but if left untreated, it usually progresses to liver failure that requires transplantation [4-6]. So treatment should be done as soon as possible, which requires timely diagnosis. There are criteria for diagnosing autoimmune hepatitis, but sometimes there is a risk of misdiagnosis, even if standard diagnostic approaches are used. The diagnosis of autoimmune hepatitis and other liver disorders, such as Wilson disease, is challenging and important and should always be considered, especially when the response to primary treatment is insufficient [7]. Although the simultaneous occurrence of Wilson disease and autoimmune hepatitis is rare [8], both can present as acute or chronic hepatitis [9]. In other words, hepatocyte necrosis and exposure of intracellular antigens to the immune system are found in Wilson disease secondary to hepatocyte necrosis, which results in low antibody titers and may confuse diagnosis and differentiation between autoimmune hepatitis and Wilson disease [8, 10].

Wilson disease is an inherited disorder of copper metabolism that occurs with an excessive increase in the accumulation of copper in organs, such as the nervous system, liver, kidneys, and heart. A wide range of symptoms follows after damaging organs caused by copper deposition [11]. Wilson disease has been reported in different age groups from 3 to 50 years. The disease manifests as hepatic (about 40%), neurological (about 40%), mental (about 20%), and in rare cases (less than 10%), as hemolytic anemia. Hepatic manifestations include autoimmune hepatitis, recurrent jaundice, hepatitis, hepatic impairment, and chronic liver disease [12]. Wilson disease is a genetic disorder that can be successfully controlled if diagnosed and treated correctly and timely, but if left untreated, it can be fatal [11, 13, 14]. Early diagnosis and treatment, especially in acute liver failure, is important to protect against disease progression and cirrhosis or liver failure because prompt treatment allows serum copper to be removed and the pa-

tient to be stabilized to facilitate orthotopic liver rescue transplantation [13]. However, one of the challenges that clinicians face when managing patients with liver failure is the immediate reassurance of diagnosis of Wilson disease to facilitate patient survival because clinical manifestations of Wilson disease can vary widely. Sometimes due to the overlap of clinical manifestations of this disease with other diseases such as autoimmune hepatitis, its diagnosis becomes complicated and often delayed [15-17], resulting in unpleasant consequences. On the other hand, patients with acute liver failure due to autoimmune hepatitis, unlike patients with acute liver failure due to Wilson disease, may respond better to medical treatment with immunosuppressive agents, if diagnosed and treated promptly. This treatment can eliminate the need for liver transplants [18].

In general, in this group of patients who have Wilson disease and autoimmune hepatitis simultaneously, there are features of the patient, disease, and laboratory and histopathological studies that may be misleading. Therefore, identification of these features in rare patients who have both Wilson disease and autoimmune hepatitis is necessary for relevant specialists to adopt appropriate treatment [10].

A review of the available databases found that most studies on the simultaneity of Wilson disease and autoimmune hepatitis are case reports [7-10, 15], and no systematic review study was found for a comprehensive review. Therefore, to obtain stronger and more reliable evidence in this field and due to the importance of correct and timely diagnosis and subsequent appropriate treatment of these two diseases to maintain patient survival, this study was conducted to determine features of the patient, disease, diagnostic studies, and therapeutic measures in cases of simultaneity of Wilson disease and autoimmune hepatitis so that the results could be an appropriate clinical guide for specialists.

2. Materials and Methods

The present systematic review study was conducted to review the comorbidity of autoimmune hepatitis and Wilson disease according to PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (2021). The research question in the present study was designed based on PICO (Patient/Problem, Intervention, Comparison, and Outcome) components. The details of how to use PICO components, given that most of the studies were of the case report studies, are as follows:

P: Population/ Disease/ Problem: Patients with the simultaneity of Wilson disease and autoimmune hepatitis

I: Intervention: Therapeutic measures (dose, frequency, and duration), diagnostic tests (type and frequency), and risk factors for the simultaneity of Wilson disease and autoimmune hepatitis

C: Comparison: not applicable in this study

O: Outcome: Response to treatment (death, liver transplant, treated, etc.)

Data sources

To find evidence related to the study purpose objectives, Persian language databases, such as Barakat knowledge network system, SID, and Magiran, and international databases, such as Google Scholar, Web of Science, ProQuest, Springer, ScienceDirect, Medline via PubMed, and Scopus were searched with keywords specified in the title of the articles. The databases were searched with no time limit until the end of February 2016. In addition, the Civilica database was searched to find abstracts of articles presented at national and international congresses to include articles related to the purpose of the study. For a complete search, the final references of the obtained articles were also investigated. Two researchers conducted the search independently. The keywords specified for searching Persian and English language databases included "Wilson disease", "hepatitis", and "autoimmune", which were used by MeSH strategy and Boolean operators (AND & OR). The search strategy is presented in [Table 1](#).

Inclusion and exclusion criteria

The inclusion criteria in the present review study included 1) the study was observational such as case report, case series, cross-sectional, group, and case-control studies, and 2) the study was published in Persian or English. The exclusion criteria included low-quality studies based on the score obtained from the checklist.

The quality of case report studies was evaluated using the instrument proposed by Murad et al. [19]. The instrument consists of eight questions in four dimensions, including selection, ascertainment, causality, and case report, each of which is given a score of 0 or 1. The maximum possible score for a study based on this instrument is eight. Of course, no cut-off point is considered for this instrument, and qualitative evaluation of the study and observance of the dimensions proposed in

this instrument is considered more. In case of disagreement at all stages of primary and secondary screening, evaluation of article quality, and selection of studies, the third researcher was used to resolve existing differences and control bias.

The STROBE (the Strengthening the Reporting of Observational Studies in Epidemiology) statement checklist was also considered to assess the quality of observational studies, such as cross-sectional, cohort, and case-control studies. The STROBE checklist consists of 22 different sections and evaluates various aspects of the methodology, including sampling methods, measurement of variables, statistical analysis, adjustment of confounders, the validity and reliability characteristics of the tools used, and the objectives of the study. Each item is given a score of 0 or 1. In this checklist, the minimum score was considered 15.5 [17]. However, because the studies related to the purpose of the study were of the case report type, this checklist was not used, and the specific checklist pertaining to the case report studies was used.

Study selection

By searching databases, 218 studies were finally identified and reviewed after excluding duplicates during primary and secondary screening. So that in the first screening, titles and abstracts were reviewed; 15 articles remained after this stage. In the secondary screening, the full text of the articles was also evaluated by two researchers. At this stage, 5 articles were excluded from the review process due to inadequacy and ambiguity of information and publication in languages other than English or Persian. For example, one of the studies [17], despite reporting information on diagnostic tests and clinical manifestations of 10 patients (reporting information as a percentage and not reporting information on each case in detail), was excluded for reasons, such as not reporting the age of participants, diagnosis direction, treatment measures, and patient outcomes. Therefore, after this stage, 10 articles were evaluated in terms of quality. Because of the proper quality of the articles, no study was excluded, and finally, 10 studies entered the review process. The details are given in [Figure 1](#).

Data extraction

To extract information from studies, a checklist was designed that included the patient age and gender, reference, diagnosis direction (Wilson disease to autoimmune hepatitis or vice versa), clinical manifestations at primary diagnosis, preliminary diagnostic tests, primary therapeutic measures, duration of primary diagnosis to

secondary diagnosis, clinical manifestations at secondary diagnosis, secondary diagnostic tests, secondary therapeutic measures, and outcomes.

Finally, after extracting the data, the quantitative data obtained from studies, including patient age, and duration from primary to secondary diagnosis, were summarized and analyzed using descriptive statistics such as Mean±SD. Also, the qualitative data, including patient gender, diagnosis direction, and outcomes, were summarized and analyzed using descriptive statistics such as frequency (number and percentage).

3. Results

In the present study, 10 studies were included in the review process. The details of study selection are given in [Figure 1](#).

Study characteristics

Out of 10 studies, there were 8 case reports [7, 9, 10, 18, 20-23], 1 opinion study [24], and 1 letter to the editor [25]. So that 6 case report studies, 1 opinion study, and the letter to the editor reported one case [9, 10, 18, 20, 22-24]. The other two studies reported two [21], and four cases [7], respectively.

In general, this review study reported information on 14 patients with comorbidity of Wilson disease and autoimmune hepatitis. The age range of patients was between 5 and 48 years, and the Mean±SD age of participants in the study was 19±11 years. Eight (57%) out of 14 participants were female. Diagnosis direction was autoimmune hepatitis to Wilson disease in 8 cases [7, 9, 21, 23, 24], and reverse in 3 cases [7, 20, 22]. In three cases [10, 18, 25], the simultaneity of Wilson disease and autoimmune hepatitis was considered from the beginning with no primary and secondary diagnosis. Finally, out of 8 patients [7, 15, 21, 23, 24] diagnosed with autoimmune hepatitis to Wilson disease, in two cases [9, 23], the primary diagnosis of autoimmune hepatitis was rejected.

In another case [24], the primary diagnosis of autoimmune hepatitis was not rejected and remained. In three cases [7, 20, 22] with the diagnosis of Wilson disease to autoimmune hepatitis, in one case [22] primary diagnosis of Wilson disease was rejected. In another case [20], the primary diagnosis of Wilson disease was not rejected and remained. It should be noted that in other studies, no explanation was given regarding rejection or non-rejection of primary diagnosis. The duration from primary diagnosis to secondary diagnosis varied from

one month to three years [7, 9, 20, 21, 24], although in some studies, this time has not been reported [22, 23].

Primary clinical manifestations reported in patients with early diagnosis of autoimmune hepatitis were nausea [9], vomiting [7], abdominal pain [7, 23], lethargy [9], fatigue, lethargy, skin rash, foot edema, pruritus [21], jaundice [21, 23], hepatomegaly [7], abdominal distension [23], and mild tremor [9]. Secondary clinical manifestations in patients with a secondary diagnosis of Wilson disease included severe encephalopathy, hand tremor [24], jaundice, ascites, advanced Cushing syndrome features [21], psychiatric (depression), and neurological symptoms (bradykinesia, gait disorders, visual acuity disorders) [7].

Primary clinical manifestations reported in patients with early diagnosis of Wilson disease included anorexia, weight loss, reduced concentration, aggressive behavior, epistaxis [20], fatigue, jaundice, dark urine, and pale stools [22]. Secondary clinical manifestation in patients with a secondary diagnosis of autoimmune hepatitis included jaundice [22].

Clinical manifestations in patients with the simultaneity of Wilson disease and autoimmune hepatitis (with no primary and secondary diagnosis) included nausea, vomiting, tea color urine [10], fever, jaundice, fatigue [25], coagulopathy, jaundice, ascites, and bilateral leg edema [18].

In almost all patients, diagnostic tests included complete blood count, kidney and liver function tests, prothrombin time, International Normalized Ratio (INR), and viral markers for hepatitis A, B, C, and E. More specific primary diagnostic tests in patients with primary diagnosis of autoimmune hepatitis and Wilson disease include cases, such as Anti-Nuclear Antibody (ANA) [7, 9, 10, 18, 20-25], Anti-Mitochondrial Antibody (AMA) [10, 18, 20, 21, 23-25], Anti-Smooth Muscle Antibody (ASMA) [7, 9, 10, 18, 20, 21, 23, 25], anti-Liver Kidney Microsome (anti-LKM) [18, 23, 25], serum ceruloplasmin [7, 9, 10, 18, 20, 21, 24, 25], and 24-h urinary copper [7, 9, 10, 18, 20-22, 24, 25].

A summary of the most important results of the laboratory tests is given in [Table 2](#). Abdominal ultrasound was used as a diagnostic test in most studies [7, 9, 10, 17, 18, 20, 21, 23]. Liver biopsy was performed as a primary diagnostic test in patients with a primary diagnosis of autoimmune hepatitis [7, 21, 23, 24] and a secondary diagnostic test in patients with a primary diagnosis of Wilson disease [7, 20, 22]. Liver Magnetic Resonance Imaging (MRI) was used as a primary diagnostic test in a

patient with a primary diagnosis of Wilson disease [22], abdominal MRI was used as a primary diagnostic test in a patient with a primary diagnosis of autoimmune hepatitis [24], and head MRI was used as a secondary diagnostic test in 2 patients with a secondary diagnosis of Wilson disease [7, 23]. Molecular genetic testing (DNA) was performed as a secondary diagnostic test in patients with a secondary diagnosis of autoimmune hepatitis [20] and a secondary diagnosis of Wilson [7, 24].

The drug treatments for patients with a primary diagnosis of autoimmune hepatitis included 5 cases of corticosteroid [7, 9, 21, 24] and 2 cases of corticosteroids and azathioprine [7, 21], followed by Wilson disease as a secondary diagnosis for this group of patients included 5 cases of d-penicillamine [7, 9, 21, 24], 1 case of azathioprine and zinc and 5-aminosalicylic acid [7] that this patient had Crohn's disease.

The drug therapies adopted for patients with a primary diagnosis of Wilson disease included one case of d-penicillamine with vitamin E and pyridoxine [20]. In another case with a primary diagnosis of Wilson disease, d-penicillamine was first prescribed, and a month later, steroids were added. Four weeks later, due to severe neutropenia, d-penicillamine was discontinued, and trientine was started. Six months later, trientine was gradually reduced, and zinc therapy was started. After 7 months, low-dose glucocorticosteroid therapy was resumed [7]. Drug therapies for patients with a secondary diagnosis of autoimmune hepatitis included 2 cases of corticosteroid therapy [20, 22].

The therapeutic measures for patients with the simultaneity of Wilson disease and autoimmune hepatitis (with no primary and secondary diagnosis) included prednisolone, azathioprine, d-penicillamine [10], prednisolone, and azathioprine [25]. A patient with Wilson disease and autoimmune hepatitis [18] received prednisolone and d-penicillamine along with several blood transfusions, vitamin K, diuretics, prophylactic antibiotics, and plasmapheresis, which resulted in liver transplantation due to no improvement.

Liver transplantation was one of the successful therapeutic measures in which 3 patients [18, 21, 23] underwent liver transplantation, of which 2 [21, 23] out of 3 transplants were related to patients whose secondary diagnosis was Wilson disease. The patients' condition improved in all cases after receiving treatment or transplantation. Other details are presented in Table 3.

4. Discussion

The present study was conducted to explore features of the patient, disease, diagnostic studies, and therapeutic measures in cases of Wilson disease and autoimmune hepatitis comorbidity. According to the results of the reviewed studies, in 8 cases [7, 9, 21, 23, 24], autoimmune hepatitis was the primary diagnosis, and Wilson disease was not diagnosed at first. In some cases, it seems that patients with Wilson disease have more convincing features of autoimmune hepatitis, and even primary treatment with immunosuppressive drugs may lead to relative improvement [21]. For example, in Gromny et al. study [24], increased aminotransferases, ANA positive, hypergammaglobulinemia, and negative viral markers were possible reasons for early diagnosis of autoimmune hepatitis.

In another study [7], 3 patients with a primary diagnosis of autoimmune hepatitis were reported, so that in the first patient, possible reasons, such as ANA positive, high IgG, and liver cell fibrosis, led to the primary diagnosis of autoimmune hepatitis only. In the second patient, ASMA and ANA were positive and severe inflammation, and fibrosis of liver cells were the only causes of primary diagnosis of autoimmune hepatitis. However, six months after primary diagnosis of autoimmune hepatitis, serum ceruloplasmin levels, and mutations were detected in molecular genetic testing and psychiatric (depression) and neurological (bradykinesia, gait disorders, visual acuity disorders) symptoms led to the secondary diagnosis of Wilson disease. In the third patient in the above study [7], serum ceruloplasmin and urinary copper were normal at baseline, and primary diagnosis of autoimmune hepatitis was made based on ANA positive, periportal inflammation, and severe steatosis.

In Santos et al. study [9], due to an increase in aminotransferases and bile enzymes, negative viral markers, ANA positive, and liver dysfunction, a primary diagnosis of autoimmune hepatitis was proposed. In Milkiewicz et al. study [21], an increase in aminotransferases and ASMA and ANA positive was one of the possible reasons for primary diagnosis of autoimmune hepatitis. Also, the clinical manifestations similar to autoimmune hepatitis and normal serum ceruloplasmin levels were possible reasons for the late diagnosis of Wilson disease.

In general, for justifying primary diagnosis of autoimmune hepatitis only in the above studies [7, 9, 21, 24], it can be said that the presence of autoantibodies, hypergammaglobulinemia, increased aminotransferases and negative viral markers are among the criteria for auto-

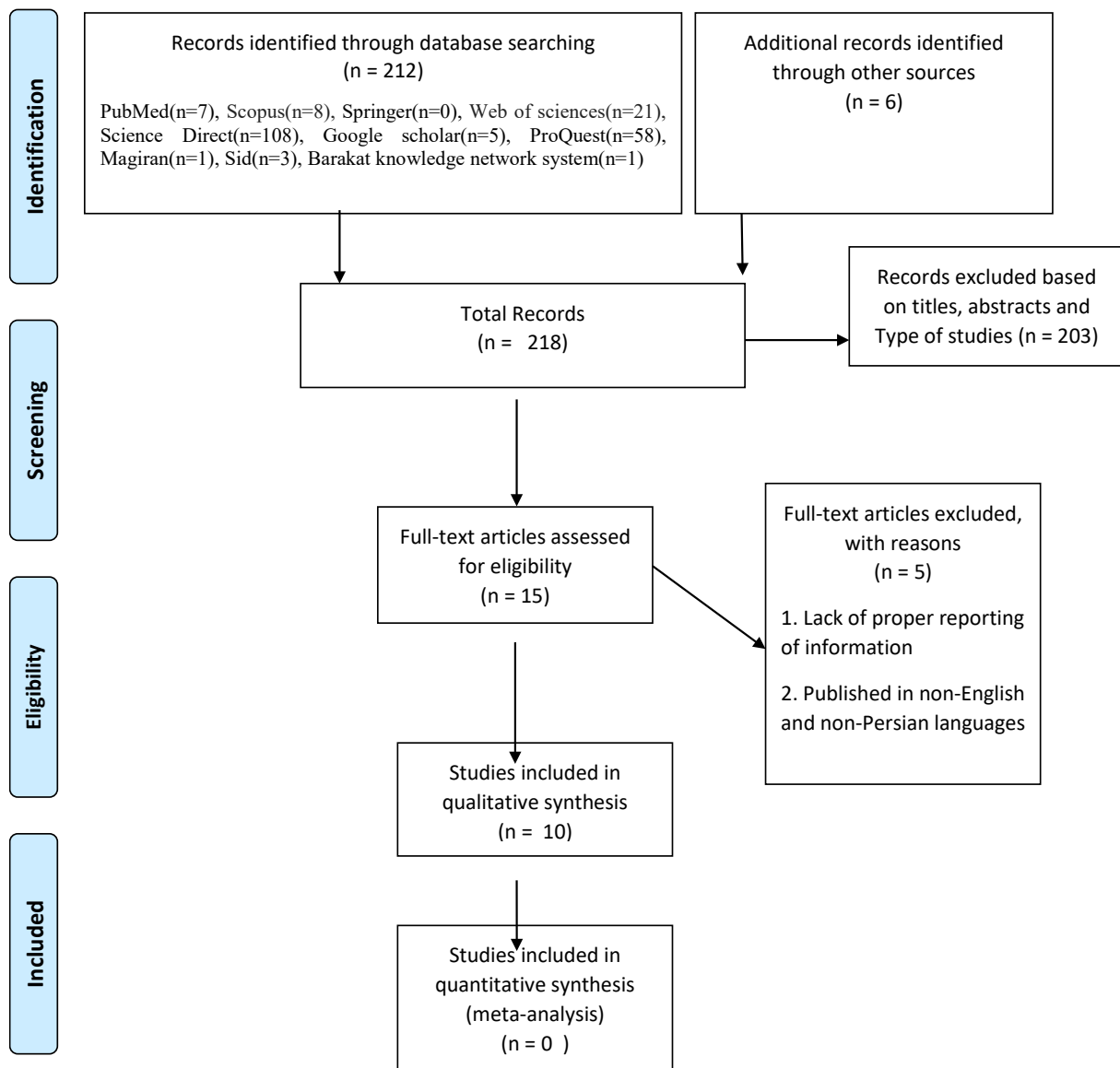


Figure 1. Flowchart of studies selection

immune hepatitis diagnosis [15]. Therefore, the presence of any of the criteria in some patients with Wilson disease may be considered as misleading possible reasons for diagnosis. On the other hand, ANA and ASMA are recommended tests for diagnosing autoimmune hepatitis, but they are not specific because they can be diagnosed in children with other diseases, such as viral infections, celiac disease, and Wilson disease [18].

The role of antibodies in Wilson disease can be due to necrosis of liver cells or another disease as one of the primary features of its pathological mechanism [8, 9] that sometimes the presence of strong and prominent auto-

immune features may lead to the exclusion of accurate screening for Wilson disease. Therefore, screening for Wilson disease should be considered, especially when a poor response to steroid therapy is seen in patients with autoimmune hepatitis. In this regard, diagnostic tests are suggested, such as serum ceruloplasmin, 24-h urinary copper, albumin level, molecular genetic testing (DNA), MRI, liver biopsy, and Kayser-Fleischer ring eye examination for more detailed evaluation and more accurate diagnosis. Regarding clinical manifestations, although most of the clinical manifestations of patients, such as nausea, vomiting, hepatomegaly, fatigue, and jaundice, overlap in two diseases and can be mislead-

Table 1. Search strategy

Database	Search
PubMed	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])
Scopus	(TITLE(Wilson Disease) OR TITLE(Wilson’s Disease) AND TITLE (Autoimmune) AND TITLE(Hepatitis))
Springer	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])
Web of Science	(TI=(Wilson Disease* OR Wilson’s Disease* AND Autoimmune* AND Hepatitis))
Science Direct	((Wilson Disease OR Wilson’s Disease[Title]) AND (Autoimmune[Title]) AND (Hepatitis[Title]))
Google Scholar	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])
ProQuest	TI(Wilson Disease OR Wilson’s Disease) AND Autoimmune AND Hepatitis
Magiran	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])
SID	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])
Barakat knowledge network system	((Wilson Disease[Title] OR Wilson’s Disease[Title])) AND (Autoimmune[Title]) AND (Hepatitis[Title])

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ing, regarding symptoms such as psychiatric symptoms (depression) and neurological (bradykinesia, gait disorders, and visual acuity disorders) symptoms can also help diagnose Wilson disease.

Liver transplantation was one of the therapeutic measures performed successfully for 3 patients [18, 21, 23]. However, 2 cases [21, 23] of 3 transplants were related to patients whose secondary diagnosis was Wilson disease. Therefore, early diagnosis of Wilson disease is very important because if diagnosis of Wilson disease is delayed, there is a possibility of liver transplanta-

tion. Therefore, correct evaluation and diagnosis in this group of patients is also important because if diagnosed early in patients with autoimmune hepatitis and Wilson disease, liver transplantation will usually be prevented. Thus, simultaneous administration of prednisolone, azathioprine, and d-penicillamine may improve the patient’s condition [10].

In some studies [7, 20, 22], Wilson disease was a primary diagnosis, and autoimmune hepatitis was not diagnosed. A possible reason for delayed diagnosis of autoimmune hepatitis is the result of diagnostic tests. In

Table 2. Summary of laboratory test results

Direction of Diagnosis	ALT/ Primary test (Min-Max)	AST/ Primary test (Min-Max)	ALP/ Primary test (Min-Max)	Serum Ceruloplasmin / Primary test (Min-Max)	24-hour Urinary Cu/ Primary test (Min-Max)	ANA/ Primary test	ASMA/ Primary test	ALT/ Secondary test (Min-Max)	AST/ Secondary test (Min-Max)	ALP/ Secondary test (Min-Max)	Serum Ceruloplasmin/ Secondary test (Min-Max)	24-hour Urinary Cu/ Secondary test (Min-Max)	ANA/ Secondary test	ASMA/ Secondary test
AIH & WD (N=3)	34-2327 U/L (n=3)	67-1219 U/L (n=3)	143-286 U/L (n=3)	0.2-20 mg/dL (n=3)	855-1600 µg (n=3)	Pos. (n=3)	Pos. (n=2)	27 U/L (n=1)	38 U/L (n=1)	54 U/L (n=1)	-	-	-	-
AIH to WD (N=8)	56-510 U/L (n=7)	83-522 U/L (n=7)	21-380 U/L (n=2)	24-40 mg/dL (n=2)	23-50 µg (n=3)	Pos (n=7)	Neg. (n=1)	69 U/L (n=1)	72 U/L (n=1)	247 U/L (n=1)	0.11-19 mg/dL (n=4)	23-659 µg (n=4)	Neg. (n=1)	Neg. (n=1)
WD to AIH (N=3)	345-1002 U/L (n=2)	336-475 U/L (n=2)	178-1116 U/L (n=2)	16 mg/dL (n=1)	236-4901 µg (n=2)	-	-	1925 U/L (n=1)	1203 U/L (n=1)	448 U/L (n=1)	-	85 µg (n=1)	Pos. (n=2)	Pos. (n=3)

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AIH: Autoimmune Hepatitis; WD: Wilson Disease; ALT, Alanine Transaminase; AST: Aspartate Aminotransferase; ANA: Anti-Nuclear Antibody; ASMA: Anti-Mitochondrial Antibody; ASMA: Anti-Smooth Muscle Antibody. n: number of patients

a study [7], the Kayser-Fleischer ring was seen on ocular examination, and changes in serum ceruloplasmin and 24-h urinary copper led to the primary diagnosis of Wilson disease only. In Dara et al. study [20], an increase in 24-h urinary copper and clinical manifestations, such as low concentration and aggressive behaviors of the patient, were among the possible reasons for primary diagnosis of Wilson disease only because patients with Wilson disease could refer with neurological disorders and psychiatric symptoms [13].

In general, for justifying the cause of primary diagnosis of Wilson disease in the other studies mentioned above [7, 20], it may be possible to point out significant cases for diagnosis of Wilson disease. For example, 24-h urinary copper is one of the tests considered for patients with Wilson disease. This test is abnormal in 80%-85% of untreated patients with Wilson disease, although abnormal copper metabolism may occur [25, 26]. During the review of studies in the present review, 24-h urinary copper was lower in studies with a secondary diagnosis of Wilson disease [7, 9, 21, 23, 24] than in studies

with a primary diagnosis of Wilson disease [7, 20, 22], which probably is a factor of delayed diagnosis of Wilson disease. Kayser-Fleischer ring is also found in 50% of diagnoses of Wilson disease, but in some cases in Wilson disease, Kayser-Fleischer ring may not be present in the eye examination, and there is no history of neuropsychiatric symptoms. Low ceruloplasmin levels are seen in most patients with neurological Wilson disease, but it may be within the normal range in about half of patients with liver Wilson disease [27]. In view of the above, screening for autoimmune hepatitis in patients with a primary diagnosis of Wilson disease should be considered. In this regard, it is suggested to perform diagnostic tests such as serological tests, ANA, ASMA, AMA [7, 9, 10, 18, 20, 21, 23], Anti-LKM, complement level, gamma globulin, IgG, albumin, molecular genetic tests (DNA), MRI, and liver biopsy for more accurate assessments and diagnosis.

Table 3. Characteristics of studies (n=10)

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome
Dara et al. (2015) [10]	Iran	10 years old/ Male	AIH & WD	Nausea, vomiting, and tea-color urine	Physical exam: spleen was not palpable, although mild hepatomegaly/KF ring (+) Lab tests: Hb: 8.9 g/L Plt: 151×10 ³ /μL Bilirubin (total, Direct): 7.3, 2.5 mg/dL PT: 19.5 s INR: 2.02 ESR: 54 mm/h Alb: 3 g/dL Globulin: 4.9 g/dL AST: 139 mg/dL* ALT: 133 mg/dL* ALP: 286 IU/L* ANA: 1/160 AMA: 1/160 ASMA: 1/80 Anti-LKM1: 1/20 Ceruloplasmin: 0.2 g/L 24-h urine copper: 1600 mc/d* Hepatitis markers (HBV, HAV, HCV): :- Liver biopsy: fibrous bands encircling clusters of hepatocytes and regenerative nodules	oral prednisolone (1 mg/kg/day) and azathioprine (1 mg/kg) and d-penicillamine	-	-	-	-	Liver enzymes changed to near normal levels, after 6 months of medical therapy

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome
Loudianos et al. (2016) [18]	Italy	15 years old/ Female	AIH & WD	Coagulopathy, jaundice, ascites, and bilateral leg edema	<p>Physical exam: Conscious and oriented adolescent, jaundiced with mild ascites/ palpable liver and spleen/ KF ring (+)</p> <p>Lab tests: Hb: 9.1 g/dL* Hct: 25 %* PLT: 73× 109/L* PT: 34.2s* INR: 2.76* DB: 4.4 mg/dl* TB: 10.7 mg/dL* AST: 67 IU/L* ALT: 34 IU/L ALP: 143 IU/L γGT: 47 IU/L* Alb: 3.1 mg/dL* ANA: + ASMA: + AMA: + Anti-LKM1: - Hepatitis markers (HBV, HAV, HCV): - Serum copper: 65 mg/dL urinary copper: 1600 mg/24-h* IgG: 2970 mg/dL Serum ceruloplasmin: 13.7 mg/dL* Liver copper content: 388 mg Cu/g dry tissue* DNA analysis of ATP7B: compound heterozygous state for the already described c.2532delA and c.3061-1 G->A mutations Liver biopsy: diffuse parenchymal remodeling with severe lobular disarray, nodular regeneration with hepatocyte ballooning, neocholangiolar proliferation, diffuse lymphocyte infiltrates with the formation of nodular lymphocyte aggregates with T-cell phenotype, and plasma cell infiltrate -Second follow-up: Lab tests: Hb: 7.1g/dL* Hct: 20.1 %* PLT: 38× 109/L* PT: 83s* INR: 3.63* AST:38 IU/L ALT:27 IU/L ALP: 54 IU/L Alb: 2.7 mg/dL* Serum ammonia: 82 mg/dL* MRI: hepatocerebral degeneration</p>	<p>Prednisone 60 mg/d and initial penicillamine dose 150 mg/d that was gradually increased to 750 mg/d, multiple blood transfusions and vitamin k Administration; diuretics, antibiotic prophylaxis, and plasmapheresis</p>		<p>Her condition deteriorated with signs of sleepiness</p>		<p>Orthotic liver transplantation</p>	<p>Successful orthotic liver transplantation</p>

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome	
Deutsch et al. (2013) [25]	Greece	32 years old/ male	AIH & WD	Fatigue, low-grade fever, and jaundice	<p>Physical exam: liver was slightly enlarged, painless, without tenderness on palpation, and with splenomegaly/ KF ring (+)</p> <p>Lab tests:</p> <p>Normal blood count</p> <p>ESR: 29 mm/1-h*</p> <p>AST:1219 IU/L*</p> <p>ALT:2327 IU/L*</p> <p>γGT:59 IU/L*</p> <p>ALP:172 IU/L*</p> <p>TB:29 mg/dL (direct: 24 mg/dL)*</p> <p>Prothrombin time: 19 s</p> <p>INR: 2</p> <p>Total proteins: 7.9 g/dL</p> <p>Alb: 3g/dL</p> <p>Hepatitis markers (HBV, HAV, HCV): -</p> <p>ANA: +</p> <p>Serum ceruloplasmin:20 mg/dL</p> <p>Serum copper: 390 μg/dL*</p> <p>free copper: 315μg/dL*</p> <p>urine copper: 855 μg/24-h*</p> <p>Liver biopsy: interface hepatitis, portal invasion with mononuclear cell infiltrate and absence of fibrosis</p> <p>Histochemical analysis with Rhodanine and Orcein: -</p> <p>Molecular genetic analysis: -</p>	<p>Prednisolone 60 mg/d and azathioprine 75 mg/d</p>	-	-	-	-	-	<p>After three years, the patient is in good health and continues on maintenance therapy with prednisolone 2.5 mg/d and Azathioprine 75 mg/d</p>
Santos et al. (2019) [9]	Brazil	25 years old/ Female	AIH to WD	Nausea, asthenia	<p>Physical exam: mild tremor of the extremities/ KF ring (+)</p> <p>Lab tests:</p> <p>AST: 109 U/L*</p> <p>ALT: 56 U/L</p> <p>ALP: 380 U/L*</p> <p>Alb: 2.4 g/dL*</p> <p>Bilirubin:1.1mg/dL</p> <p>INR: 2.62</p> <p>ANA: -</p> <p>ASMA: -</p> <p>GGT: 81 U/L*</p>	<p>Prednisone</p>	<p>8 weeks</p>	-	<p>AST: 72 U/L*</p> <p>ALT: 69U/L</p> <p>ALP: 247U/L*</p> <p>Alb:2.30* g/dL</p> <p>Bilirubin: 1.0 mg/dL</p> <p>INR: 2.20</p> <p>ANA: -</p> <p>ASMA: -</p> <p>Ceruloplasmin: 3.4 mg/Dl*</p> <p>Urinary copper: 659 μg/24-h*</p> <p>GGT: 115 U/L*</p> <p>*Reject primary diagnosis</p>	<p>D-penicillamine and interrupted prednisone</p>	<p>Treated</p>	
Zabolotsky et al. (2014) [23]	Philadelphia	48 years old/ Female	AIH to WD	Abdominal pain and distention, and scleral icterus	<p>Physical exam: scleral icterus</p> <p>Lab tests:</p> <p>AST: 522 U/L*</p> <p>ALT: 510 U/L*</p> <p>TB: 10 mg/dL</p> <p>Abdominal US: liver cirrhosis</p> <p>Transjugular hepatic biopsy: a pathological diagnosis of autoimmune hepatitis with liver parenchymal fibrosis and collapse</p>	<p>Orthotopic liver transplantation</p>	-	-	<p>Studies on the explanted liver exhibited large quantities of copper, consistent with a diagnosis of WD</p> <p>*Reject primary diagnosis</p>	-	<p>Orthotopic liver transplantation</p>	

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome
Gronny et al. (2019) [24]	Poland	30 years old/ Male	AIH to WD	-	Physical exam: KF ring (+) Increased level of AST* and ALT* Cholestatic parameters: Normal Alb: Normal PT: Normal Hepatitis markers (HBV, HAV, HCV): - Hypergammaglobulinemia Serum elevated IgG ANA: + Liver biopsy: piecemeal necrosis, interface hepatitis with lymphoplasmacytic infiltration, and bridging fibrosis in nearly all portal tracts MRI of the abdomen: enlarged liver with micronodular surface and regenerative nodules	Steroids	Three years	Hand tremors	Physical exam: KF ring (+) Lab tests: -Genetic testing: ATP7B mutation -Head MRI: hyperintensity in bilateral basal ganglia -Decreased serum ceruloplasmin simultaneously -Normal level of 24 hours urinary copper *Without rejecting the primary diagnosis	Penicillamine	-
Milkiewicz et al. (2000) [21]	The United Kingdom	15 years old/ female	AIH to WD	Progressive lethargy, jaundice, skin rash, bilateral leg swelling, pruritus	Physical exam: a young girl with cushingoid features including acne and abdominal striae, marks of excoriation, icterus, ascites, and pedal edema AST: 103 U/L* ALP: 463 U/L* Bilirubin: 65 mmol/L* Alb: 22 g/L* INR: 2.2 IgG: 14 g/L PLT: 113x109/mL ANA: + AMA: - complement C3: 0.43 g/L complement C4: 0.16 g/L Hepatitis markers (HBV, HAV, HCV): - Ultrasound scan: irregular, cirrhotic liver, patent portal, and hepatic veins and ascites Liver biopsy: cirrhosis with interface hepatitis	Prednisolone at a dose of 30 mg/d	One month	-	Ceruloplasmin: 0.11 g/L* serum copper: 11 mg/L* copper in 24 h urine: 213 mg* Amount of copper in the dry liver: 385 mg/g	D-penicillamine was begun at 125 mg/d orally and was gradually increased up to 750 mg/d, accompanied by a tapering of the prednisolone dose as her condition was improved	Treated
Milkiewicz et al. (2000) [21]	The United Kingdom	24 years old/ female	AIH to WD	General malaise, tiredness, and right upper quadrant pain	AST: 165 U/L* ALP: 339U/L* Bilirubin: 33 mmol/L Albumin: 29 g/L* INR: 1.5 SMA: + ANA: + AMA: - IgG: 24.6 g/L Serum ceruloplasmin: 40 mg/dL Liver biopsy: interface hepatitis	Steroid and AZT	Two years	Advanced cushingoid features, icterus, and ascites	AST: 193 U/L* Bilirubin: 219 mmol/L ALP: 581 U/L* ANA: + SMA: + Serum ceruloplasmin: 0.18 g/L* 24-h urinary copper: 326 mg* Liver US: a small coarse reflective liver consistent with cirrhosis, normal portal vein, and hepatic artery, and moderate ascites	Liver transplant	Liver transplant

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome
Naorniakowska et al. (2020) [7]	Poland	13 years old/ female	AIH to WD	Stomach pain	AST: 83 U/L* ALT: 123 U/L* GGTP: 69 U/L* Hepatitis markers (HBV, HAV, HCV): - Liver biopsy: steatohepatitis and fibrosis ANA: + Gamma globulins: 14.98 g/ IgG:2824.5 mg*	Glucocorticosteroids (GC's) and AZT	One year	-	Ceruloplasmin < 7 mg/dL* Urine copper: 151.2 µg* Liver tissue: 736.8 µg/g* molecular investigation: 2 mutations	Penicillamine	Treated
Naorniakowska et al. (2020) [7]	Poland	11 years old/ male	AIH to WD	Stomach pain and vomiting	Lab test: AST: 313 U/L* ALT: 231 U/L* ANA: 1 : 640 ASMA: 1 : 160 Hepatitis markers (HBV, HAV, HCV): - Unconjugated hyperbilirubinemia US: hepatomegaly with portal hypertension Severe inflammation, severe fibrosis Ceruloplasmin: 40 mg/dL Urine copper: 23 µg/24 h	Prednisolone	One year	developed psychiatric (depressive) and neurological symptoms (bradykinesia, gait abnormalities, visual acuity disturbances)	Ceruloplasmin: 19 mg/dL Urine copper: 23 µg/24-h molecular investigation: 1 mutation Brain MRI: specific abnormalities (hypertensive focus in T2 images in the globus pallidus)	Zinc, AZT and 5-amino-salicylic acid (5-ASA)	Treated
Naorniakowska et al. (2020) [7]	Poland	5 years old/ female	AIH to WD	-	AST: 125 U/L* ALT: 205 U/L* ANA: + ASMA: + Liver biopsy: periportal inflammation, severe steatosis with no cholestasis Ceruloplasmin: 24 mg/dL Urine copper: 50 µg/24-h	Prednisolone	One year	-	Ceruloplasmin: 14 mg/dL* liver-copper concentration: 879 µg/g* molecular investigation: 2 mutations*	Penicillamine was initiated, and after one year, steroids were withdrawn	Normal liver function test results
Dara et al. (2018) [20]	Iran	6 years old/ male	WD to AIH	Epistaxis, anorexia, weight loss (about 10 kg) since 3 years before the current presentation, poor concentration and aggressive behavior	Physical exam: normal liver size and span/KF ring (-) Lab tests: Hb: 11.9 g/dL* AST: 475 U/L* ALT: 345 U/L* ALP: 1116 IU/L* TP: 7.4 g/dL* Alb: 4.8 g/dL* TB: 1.02 mg/dL DB: 0.10 mg/dL LDH: 605 IU/L CPK: 5077 U/L Golb: 2.6 g/dL Bilirubin: 1.1 INR: 1.5	D-penicillamine with an initial dose of 125 mg every 12 hours (10 mg/kg/d), 40 mg of oral pyridoxine daily, and 400 mg of vitamin E daily with a gradual increase in D-penicillamine dose to a maximum of 250 mg dose divided into a three-course regimen	Five months	Liver function test, CPK, and LDH did not show any improvement over 5 months of treatment	AMA: - ANA: 1/640 ASMA: 1/80 Anti-LKM: - Urine 24-h copper: 107 mcg/24-h* Ceruloplasmin: 4 mg/dL Hepatitis markers (HBV, HAV, HCV): - Liver biopsy: no evidence of significant interface hepatitis DNA study: homozygote deletion in the ATP7B gene for a variant defined as c.1924G>C *Without rejecting primary diagnosis.	40 mg prednisolone (2 mg/kg/d) divided into three-course regimen doses with reduction of the dose to 5 mg after 2 months	After a year of regular follow-up, all clinical symptoms improved

Author (year) (Ref.)	Country	Age/ Gender	Direction of diagnosis	Primary Clinical Manifestation	Primary Diagnosis Tests	Primary Treatment	Duration From Primary to Secondary Diagnosis	Secondary Clinical Manifestation	Secondary Diagnosis Tests	Secondary Treatment	Outcome
Rezk et al. (2015) [22]	The United States	19 years old/ male	WD to AIH	First asymptomatic but then fatigue, jaundice, dark urine, and pale stools	Lab tests: AST: 336 U/L* ALT: 1002 U/L* ALP: 178U/L TB: 0.77 mg/dL DB: 0.43 mg/dL INR: 1.1 Alb: 3.6 g/dL IgA: 177 mg/dL IgG: 1164 mg/dL Acute hepatitis panel, CMV and EBV serologies: - AMA: - ASMA: - ANA: - Gamma globulins: - Liver MRI: hepatomegaly with periportal tracking 24-h urinary Cu: 236 µg*	-	-	Jaundice	Physical exam : jaundice/ KF(+) Lab tests: ALT: 1925 U/L* AST: 1203 U/L* ALP: 448 U/L* GGT: 232 U/L* TB: 8.7 mg/dL* DB: 5.8 mg/dL* INR: 0.97 Alb: 3.8g/dL, alpha-1 antitrypsin: 219 mg/dL ASMA: 25.3 units 24-h urinary Cu: 85 µg* Liver biopsy: portal triads with dense lymphoplasmacytic infiltrates with moderate to severe interface hepatitis *Reject Primary diagnosis	Prednisone	Notable clinical improvement
Naorniakowska et al. (2020) [7]	Poland	15 years old/ female	WD to AIH		KF ring (+) ceruloplasmin: 16 mg/dL Urine copper: 4901 µg molecular investigation: 2 mutations	Penicillamine	-	-	ANA: + ASMA: + IgG: 15.4 g/L* Liver biopsy: steato-hepatitis and fibrosis	Steroids were added/ After the next 4 weeks, trientine was initiated, and penicillamine was withdrawn. Six months later, we gradually reduced trientine and started zinc therapy. After the next 7 months, low-dose glucocorticosteroids (GC's) therapy was resumed	

AIH: Autoimmune Hepatitis; WD: Wilson Disease; TP: Total Protein; Alb: Albumin; Glob: Globulin; ALT: Alanine Transaminase; AST: Aspartate Aminotransferase; TB: Total Bilirubin; DB: Direct Bilirubin; Alkp: Alkaline phosphatase; LDH: Lactate Dehydrogenase; CPK: Creatinine Phosphokinase; Cr: Creatinine; ESR: Erythrocyte Sedimentation Rate; Hb: Hemoglobin; INR: International Normalized Ratio; Na: sodium; PT: Prothrombin Time; PTT: Partial Thromboplastin Time; GGT: Gamma-Glutamyl Transferase; ANA: Anti-Nuclear Antibody; AMA: Anti-Mitochondrial Antibody; ASMA: Anti-Smooth Muscle Antibody; Anti-LKM1: Anti-Liver Kidney Microsome type 1 antibody; HAV Ab: Hepatitis A Virus Antibody; HBs Ab: Hepatitis B surface Antibody; HBs Ag: Hepatitis B surface Antigen; HCV-Ab: Hepatitis C Virus Antibody; IgM: Immunoglobulin M.

5. Conclusion

In general, the comorbidity of Wilson disease and autoimmune hepatitis is uncommon but important. In the presence of symptoms in these patients, comorbidity of these two diseases should be considered. Additional assessments such as serum ceruloplasmin, 24-h urinary copper 24, molecular genetic testing (DNA), MRI, serological tests, ANA, ASMA, AMA, anti-LKM, complement level, gamma globulin, IgG, albumin, Kayser-Fleischer ring eye examination, and liver biopsy for correct diagnosis should be considered. Regarding clinical symptoms, psychiatric (depression) and neurological symptoms (bradykinesia, gait disorders, and visual acuity disorders) can help diagnose Wilson disease so that appropriate treatment can be proposed. If appropriate treatment is started for the disease with a diagnosis of Wilson or autoimmune hepatitis, but the response to treatment is insufficient, it is better to consider the simultaneous occurrence of two diseases or the initial misdiagnosis.

The limitations of the present study were the impossibility of performing meta-analysis due to heterogeneity in the results of diagnostic tests that lacked exactly equal kits and therapeutic measures. Access to articles published in other languages (except Persian and English) was also a limitation. It is suggested to conduct further studies to obtain stronger and more credible evidence in this field.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1400.115).

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Authors' contributions

Conceptualization and supervision: Peiman Nasri and Fatemeh Famouri; Methodology: Peiman Nasri and Fatemeh Famouri, Seyed Esmail Hosseini-Kordkhyli; Investigation, writing original draft, and writing review & editing: All authors; Data collection: Seyed Esmail Hosseini-Kordkhyli, Azar Jafari-Koulaee, Silva Hovsepian; Hossein Saneian, Majid Khademian; Data analysis: Peiman

Nasri and Fatemeh Famouri; Funding acquisition and Resources: Peiman Nasri, Seyed Esmail Hosseini-Kordkhyli.

Conflicts of interest

The authors declared no conflict of interest.

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