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

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Abstract

Background: Identifying the features of these two diseases in patients with simultaneity of Wilson's disease and autoimmune hepatitis is necessary for the relevant specialists to adopt appropriate treatment.

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

Methods: In order to find evidence related to the objective of this study, databases such as Barakat knowledge network system, SID, and 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 were searched. Inclusion criteria in the present review study included: 1) the study was observational, 2) the study was published in Persian or English. 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, after evaluating the quality, the qualified studies entered the review process. In order to extract information, a checklist was designed and data were extracted.

Results: Finally, 10 studies were included in the review process. Totally, information about 14 patients were reported. The Mean (SD) of the participants in the studies was 19 (11) years. Diagnosis direction was autoimmune hepatitis to Wilson's disease in 8 cases, and it was reversed in 3 cases. Simultaneity of autoimmune hepatitis and Wilson's disease was considered in 3 patients with no primary and secondary diagnosis.

Conclusion: Given that simultaneity of Wilson's disease and autoimmune hepatitis is uncommon but important, in the presence of symptoms in these patients, simultaneity of these two diseases should be considered and additional assessments such as serum ceruloplasmin, urinary copper 24 Hourly, molecular genetic testing, MRI, serological tests, ANA, ASMA, AMA, complement level, gammaglobulin, 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 not sufficient, it is better to consider the simultaneous occurrence of two diseases or the initial misdiagnosis.

Keywords: Autoimmune hepatitis, Wilson disease, Simultaneity, Review
Introduction

Autoimmune hepatitis is a chronic inflammatory disease of unknown etiology characterized by the presence of circulating antibodies, hypergammaglobulinemia, inflammatory changes in necrotic liver tissue, and a significant response to immunosuppressive therapy (1). It is said that 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's disease is challenging and very important and should always be considered, especially when the response to primary treatment is insufficient (7). Although simultaneity of Wilson's disease and autoimmune hepatitis is rare in a patient (8), both can present as acute or chronic hepatitis (9). In fact, hepatocyte necrosis and exposure of intracellular antigens to the immune system are found in Wilson's disease secondary to hepatocyte necrosis, which results in low antibody titers and may confuse diagnosis and differentiate autoimmune hepatitis from Wilson's disease (8, 10). Wilson's disease is an inherited disorder of copper metabolism that occurs with an excessive increase in accumulation of copper in organs such as the nervous system, liver, kidneys and heart, and it occurs due to the damaged organ caused by copper deposition followed by a wide range of symptoms (11). Wilson's disease has been reported from the age of 3 to over 50 years. Wilson's disease manifests as hepatic (about 40%), neurological (about 40%), mental (about 20%), and in rare cases (less than 10%) hemolytic anemia. Hepatic manifestations include autoimmune hepatitis, recurrent jaundice, hepatitis, hepatic impairment, and chronic liver disease (12). Wilson's 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 patient 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's
disease to facilitate a patient survival because clinical manifestations of Wilson's disease can vary widely. Sometimes due to the overlap of clinical manifestations of this disease with other diseases such as autoimmune hepatitis, its diagnosis is sometimes complicated and often delayed (15-17), which may have unpleasant consequences. On the other hand, patients with acute liver failure due to autoimmune hepatitis, unlike patients with acute liver failure due to Wilson's disease, may respond better to medical treatment with immunosuppressive agents, if diagnosed and treated promptly. This can eliminate the need for liver transplants (18).

In general, in this group of patients who have simultaneity of Wilson's disease and autoimmune hepatitis at the same time, there are features of a patient, disease, and laboratory and histopathological studies that may be misleading. Therefore, identification of these features in rare patients who have simultaneity of Wilson's disease and autoimmune hepatitis, it is necessary for relevant specialists to adopt appropriate treatment (10).

A review of the available databases found that most of the studies on simultaneity of Wilson's disease and autoimmune hepatitis are case reports (7-10, 15) and no systematic review study was found for a comprehensive review. Therefore, in order 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 aimed to determine features of a patient, disease, diagnostic studies and therapeutic measures in cases of simultaneity of Wilson's disease and autoimmune hepatitis so that the results could be an appropriate clinical guide for specialists.

Methods
The present systematic review study was conducted aimed to review simultaneity of autoimmune hepatitis and Wilson's disease according to PRISMA guidelines (2021). The research question in the present study was designed based on PICO components. The details of how to use PICO components in the present study, given that most of the studies were of the case report studies, are as follows:

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

I: Intervention: Therapeutic measures (dose, frequency, and duration), diagnostic tests (type and frequency) and risk factors for simultaneity of Wilson's disease and autoimmune hepatitis
C: Comparison: (not applicable in this study)
O: Outcome: Response to treatment (death, liver transplant, treated, etc.)

Data Sources

In order to find evidence related to the purpose of this study, 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 with keywords specified in the title of the articles were searched. The databases were searched with no time limit until the end of February 2016. In addition, 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 more 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's disease, hepatitis, and autoimmune, which were used by mesh strategy and Boolean operators (AND & OR). Search strategy is shown in Table 1.

Inclusion & Exclusion criteria

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. 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 Morad 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 zero or one. 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 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 zero or one. In this checklist, the minimum score to be scored was considered to be 15.5 (20). In this study, after search and screening, 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 related to the case report studies was used.

Study Selection
By searching databases, 218 studies were finally identified, which were reviewed after excluding repeats during primary and secondary screening. So that in the primary screening, titles and abstracts were reviewed, 15 articles were 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 and Persian. For example, one of the excluded studies (20), despite reporting information on diagnostic tests and clinical manifestations of 10 patients (reporting information as percentage and not reporting information on each case in detail), for reasons such as not reporting age of participants, diagnosis direction, treatment measures, and patient outcomes was excluded. Therefore, after this stage, 10 articles were evaluated in terms of quality. At quality evaluation stage of the articles, due to the proper quality of the articles, no study was excluded and finally 10 studies entered the review process. The details are given in Flowchart 1.

Data Extraction
In order to extract information from studies, a checklist including a patient age and gender, reference, disease (Wilson's disease to autoimmune hepatitis or vice versa), clinical manifestations at primary diagnosis, primary diagnostic tests, primary therapeutic measures, duration of primary diagnosis to secondary diagnosis, clinical manifestations at secondary diagnosis, secondary diagnostic tests, secondary therapeutic measures, and outcome was designed, and information were extracted.
Finally, after extracting the data, 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), and qualitative data including a patient gender,
Results
In the present study, 10 studies were included in the review process. The details are given in Flowchart 1.

Study characteristics
From 10 studies, there were 8 case reports (7, 9, 10, 18, 21-24), 1 opinion study (25) and 1 letter to the editor (26), so that 6 case report studies, 1 opinion study and the letter to the editor reported one case (9, 10, 18, 21, 23-25). The other two studies reported two (22), and four cases (7), respectively.

In general, this review study reported information on 14 patients with simultaneity of Wilson's 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 were 19(11) years, respectively. 8 out of 14 participants (57%) were female. Diagnosis direction was autoimmune hepatitis to Wilson's disease in 8 cases (7, 9, 22, 24, 25), and it was reversed in 3 cases (7, 21, 23). In three cases (10, 18, and 26), simultaneity of Wilson's disease and autoimmune hepatitis was considered from the beginning with no primary and secondary diagnosis. Finally, out of 8 patients (7, 15, 22, 24, 25) with diagnosis of autoimmune hepatitis to Wilson's disease, in two cases (9, 24) primary diagnosis of autoimmune hepatitis was rejected. In another case (25), primary diagnosis of autoimmune hepatitis was not rejected and remained. In three cases (7, 21, 23) with diagnosis of Wilson's disease to autoimmune hepatitis, in one case (23) primary diagnosis of Wilson's disease was rejected. In another case (21), primary diagnosis of Wilson's 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, 21, 22, 25), although in some studies this time was not reported (23, 24).

Primary clinical manifestations reported in patients with early diagnosis of autoimmune hepatitis include nausea (9), vomiting (7), abdominal pain (7, 24), lethargy (9), fatigue, lethargy, skin rash, foot edema, pruritus (22), jaundice (22, 24), hepatomegaly (7), abdominal distension (24) and mild tremor (9). Secondary clinical manifestations in patients with secondary diagnosis of
Wilson disease include severe encephalopathy, hand tremor (25), jaundice, ascites, advanced Cushing’s features (22), 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 (21), fatigue, jaundice, dark urine, and pale stools (23). Secondary clinical manifestations in patients with secondary diagnosis of autoimmune hepatitis included jaundice (23).

Clinical manifestations in patients with simultaneity of Wilson's disease and autoimmune hepatitis (with no primary and secondary diagnosis) included nausea, vomiting, tea color urine (10), fever, jaundice, fatigue (26), 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, 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's disease include cases such as ANA (7, 9, 10, 18, 21-26), AMA (10, 18, 21, 22, 24-26), ASMA (7, 9, 10, 18, 21, 22, 24, 26), Anti-LKM (18, 24, 26), serum ceruloplasmin (7, 9, 10, 18, 21, 22, 25, 26) and 24-h urinary copper (7, 9, 10, 18, 21-23, 25, 26). 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, 18, 20-22, 24). Liver biopsy was performed as primary diagnostic test in patients with primary diagnosis of autoimmune hepatitis (7, 22, 24, 25) and as secondary diagnostic test in patients with primary diagnosis of Wilson's disease (7, 21, 23). Liver MRI was used as primary diagnostic test in a patient with primary diagnosis of Wilson's disease (23), abdominal MRI was used as primary diagnostic test in a patient with primary diagnosis of autoimmune hepatitis (25), and head MRI was used as secondary diagnostic test in 2 patients with secondary diagnosis of Wilson's disease (7, 24). Molecular genetic testing (DNA) was performed as secondary diagnostic test in patients with secondary diagnosis of autoimmune hepatitis (21) and secondary diagnosis of Wilson (7, 25).

The drug treatments for patients with primary diagnosis of autoimmune hepatitis included 5 cases of corticosteroid (7, 9, 22, 25), and 2 cases of corticosteroids and azathioprine (7, 22), followed by Wilson's disease as secondary diagnosis for this group of patients included 5 cases of d-penicillamine (7, 9, 22, 25), 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 primary diagnosis of Wilson's disease included one case of d-penicillamine with vitamin E and pyridoxine (21). In another case with primary diagnosis of Wilson's disease, d-penicilamine was first prescribed and a month later, steroids were added. 4 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 secondary diagnosis of autoimmune hepatitis included 2 cases of corticosteroid therapy (21, 23).

The therapeutic measures for patients with simultaneity of Wilson's disease and autoimmune hepatitis (with no primary and secondary diagnosis) included prednisolone, azathioprine and d-penicilamine (10), and prednisolone and azathioprine (26). A patient with simultaneity of Wilson’s disease and autoimmune hepatitis (18) received prednisolone and d-penicilamine 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, 22, 24) underwent liver transplantation, of which 2 (22, 24) out of 3 transplants were related to patients whose secondary diagnosis was Wilson’s disease. The patients’ condition improved in all cases after receiving treatment or transplantation. Other details are presented in Table 3.

**Discussion**

The present study was conducted aimed to explore features of a patient, disease, diagnostic studies and therapeutic measures in cases of simultaneity of Wilson's disease and autoimmune hepatitis. According to the results of the reviewed studies, in 8 cases (7, 9, 22, 24, 25) autoimmune hepatitis was primary diagnosis and Wilson's disease was not first diagnosed. In some cases, it seems that patients with Wilson's disease have more convincing features of autoimmune hepatitis, and even primary treatment with immunosuppressive drugs may lead to relative improvement (22). For example, in a study by Gromny et al. (2019) (25), 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 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 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 secondary diagnosis of Wilson's 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 a study by Santos et al. (2019) (9), due to an increase in aminotransferases and bile enzymes, negative viral markers, ANA positive, and liver dysfunction, primary diagnosis of autoimmune hepatitis was proposed. In a study by Milkiewicz et al. (2000) (22), an increase in aminotransferases and ASMA and ANA positive was one of the possible reasons for primary diagnosis of autoimmune hepatitis. Also in the above study, clinical manifestations similar to autoimmune hepatitis and normal serum ceruloplasmin levels were possible reasons for late diagnosis of Wilson's disease. In general, for justifying primary diagnosis of autoimmune hepatitis only in the above studies (7, 9, 22, 25), it can be said that since the presence of autoantibodies, hypergammaglobulinemia, increased aminotransferases and negative viral markers are among criteria for autoimmune hepatitis diagnosis (15). Therefore, the presence of any of the criteria in some patients with Wilson's disease may be considered as misleading possible reasons for diagnosis. On the other hand, ANA and ASMA are recommended tests for diagnosis of 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's disease (18). The role of antibodies in Wilson's 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 autoimmune features may lead to exclusion of accurate screening for Wilson's disease. Therefore, screening for Wilson's 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 misleading, regarding symptoms such as psychiatric symptoms (depression) and neurological (bradykinesia, gait disorders and visual acuity disorders) symptoms can also help diagnose Wilson's disease.

Liver transplantation was one of therapeutic measures that was performed successfully for 3 patients (18, 22, 24). However, 2 cases (22, 24) of 3 transplants were related to patients whose secondary diagnosis was Wilson's disease. Therefore, early diagnosis of Wilson's disease is very important because if diagnosis of Wilson's disease is delayed, there is a possibility of liver transplantation. Therefore, correct evaluation and diagnosis in this group of patients is also important because if diagnosed early in patients with autoimmune hepatitis and Wilson's disease, liver transplantation will usually be prevented, so that simultaneous administration of prednisolone, azathioprine and d-penicillamine may improve the patient's condition (10).

In some of the studies (7, 21, 23), Wilson's disease was primary diagnosis and autoimmune hepatitis was not diagnosed. A possible reason for delayed diagnosis of autoimmune hepatitis is the result of diagnostic tests. In a study (7), Kayser-Fleischer ring was seen on ocular examination, and changes in serum ceruloplasmin and 24-h urinary copper led to primary diagnosis of Wilson's disease only. In a study by Dara et al. (2018) (21), 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's disease only because it was reported that patients with Wilson's disease can refer with neurological disorders and psychiatric symptoms (13). In general, for justifying the cause of primary diagnosis of Wilson's disease only in the other studies mentioned above (7, 21), it may be possible to point out significant cases for diagnosis of Wilson's disease. 24-h urinary copper is one of the tests considered for patients with Wilson's disease. This test is abnormal in 80-85% of untreated patients with Wilson's disease, although abnormal copper metabolism may occur (26, 27).

During review of studies in the present review, 24-h urinary copper was lower in studies with secondary diagnosis of Wilson's disease (7, 9, 22, 24, 25) than in studies with primary diagnosis of Wilson's disease (7, 21, 23), which probably is a factor of delayed diagnosis of Wilson's disease. Kayser-Fleischer ring is also found in 50% of diagnoses of Wilson's disease, but in some cases in Wilson's 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's disease, but may be within the normal range in about half of
patients with liver Wilson's disease (28). In view of the above, screening for autoimmune hepatitis in patients with primary diagnosis of Wilson's 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, 21, 22, and 24), Anti-LKM, complement level, gammaglobulin, IgG, albumin, molecular genetic tests (DNA), MRI, and liver biopsy for more accurate assessments and diagnosis.

**Conclusions**

In general, given that simultaneity of Wilson's disease and autoimmune hepatitis is uncommon but important, in the presence of symptoms in these patients, simultaneity of these two diseases should be considered and additional assessments such as serum ceruloplasmin, urinary copper 24 Hourly, molecular genetic testing (DNA), MRI, serological tests, ANA, ASMA, AMA, Anti-LKM, complement level, gammaglobulin, IgG, albumin, Kayser-Fleischer ring eye examination and liver biopsy for correct diagnosis should be considered. Regarding clinical symptoms such as psychiatric (depression) and neurological symptoms (bradykinesia, gait disorders, and visual acuity disorders) can help diagnose Wilson's disease so that appropriate treatment can be proposed. If appropriate treatment was started for the disease with a diagnosis of Wilson or autoimmune hepatitis, but the response to treatment was not sufficient, it is better to consider the simultaneous occurrence of two diseases or the initial misdiagnosis.

Also, among the limitations of the present study were the impossibility of performing meta-analysis due to heterogeneity in the results of diagnostic tests that did not have 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.

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**Conflict of Interest Disclosure**

We declare that we have no conflict of interest.
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Authors' Contribution
P.N performed the data analysis and wrote the manuscript. F.F, SE.H, A.J, S.H, M.KH, and H.S screened the literature, extracted the data, and assessed the quality of the paper. F.F conceived the idea and design of this study.

References
Records identified through database searching (n = 212)
PubMed(n=7), Scopus(n=8), Springer(n=0), Web of sciences(n=21), Science Direct(n=108), Google scholar(n=5), ProQuest(n=58), Magiran(n=1), Sid(n=3), Barakat knowledge network system(n=1)

Additional records identified through other sources (n = 6)

Total Records (n = 218)
Records excluded based on titles, abstracts and Type of studies (n = 203)

Full-text articles assessed for eligibility (n = 15)

1. Lack of proper reporting of information
2. Published in non-English and non-Persian languages

Studies included in qualitative synthesis (n = 10)

Studies included in quantitative synthesis (meta-analysis) (n = 0)

Flow chart 1. Process of studies selection (PRISMA flow chart)
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<th>Database</th>
<th>Search</th>
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<td>PubMed</td>
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</tr>
<tr>
<td>Scopus</td>
<td>(TITLE(Wilson Disease) OR TITLE(Wilson’s Disease) AND TITLE (Autoimmune) AND TITLE(Hepatitis))</td>
</tr>
<tr>
<td>Springer</td>
<td>(((Wilson Disease[Title]) OR (Wilson’s Disease[Title]) AND (Autoimmune[Title])) AND (Hepatitis[Title])</td>
</tr>
<tr>
<td>Web of sciences</td>
<td>(TI=(Wilson Disease* OR Wilson's Disease* AND Autoimmune* AND Hepatitis))</td>
</tr>
<tr>
<td>Science Direct</td>
<td>((Wilson Disease OR Wilson's Disease[Title]) AND (Autoimmune[Title]) AND (Hepatitis[Title]))</td>
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<td>Google scholar</td>
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<td>ProQuest</td>
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<td>Barakat knowledge network system</td>
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Table 2. Summary of laboratory test results

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

Note: n= number of patients
<table>
<thead>
<tr>
<th>Author (Year) (Ref.)</th>
<th>Country</th>
<th>Age/ Gender</th>
<th>Direction of diagnosis</th>
<th>Primary Clinical manifestation</th>
<th>Primary Diagnosis tests</th>
<th>Primary Treatment</th>
<th>Duration from primary to secondary diagnosis</th>
<th>Secondary Clinical manifestation</th>
<th>Secondary Diagnosis tests</th>
<th>Secondary Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dara et al. (2015) (10)</td>
<td>Iran</td>
<td>10 years old/ Male</td>
<td>AIH &amp; WD</td>
<td>nausea, vomiting, and tea-color urine</td>
<td><strong>Physical exam:</strong> spleen was not palpable, although mild hepatomegaly/KF ring (+) <strong>Lab tests:</strong> Hb: 8.9 g/L, Plt: 151 x 10^9/micrL, 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, 24hr Urine Copper: 1600 mc/d*, Hepatitis markers (HBV, HAV, HCV): -</td>
<td><strong>Liver Biopsy:</strong> Fibrous bands encircling clusters of hepatocytes and regenerative nodules</td>
<td>oral prednisolone (1 mg/Kg/day) and azathioprine (1 mg/kg) and D-penicillamine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Liver enzymes change to near normal levels, after 6 months of medical therapy</td>
</tr>
<tr>
<td>Loudianos et al. (2016) (18)</td>
<td>Italy</td>
<td>15 Years Old/ Female</td>
<td>AIH &amp; WD, Coagulopathy, jaundice, ascites, and bilateral leg edema</td>
<td>Physical exam: Conscious and oriented adolescent, jaundiced with mild ascites/palpable liver and spleen/ KF ring (+) <strong>Lab tests:</strong> Hb: 9.1 g/dL*, Hct: 25 %<em>, PLT: 73 x 10^9/L</em>, 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: +</td>
<td>Prednisone 60 mg/day and Penicillamin e initial dose 150 mg/day that was gradually increased to 750 mg/day, multiple blood transfusions and vitamin K Administration; diuretics, antibiotic prophylaxis, and plasmaphere</td>
<td>-</td>
<td>Her condition deteriorated with signs of sleepiness</td>
<td>-</td>
<td>Orthotic liver Transplantation</td>
<td>Successful Orthotic liver Transplantation</td>
<td></td>
</tr>
<tr>
<td><strong>ASMA:</strong> +</td>
<td><strong>AMA:</strong> +</td>
<td><strong>Anti-LKM1:</strong> -</td>
<td><strong>Hepatitis markers (HBV, HAV, HCV):</strong> -</td>
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<tr>
<td>Serum copper: 65 mg/dL</td>
<td>Urinary copper: 1600 mg/24 h*</td>
<td>IgG: 2970 mg/dL</td>
<td>Serum ceruloplasmin: 13.7 mg/dL*</td>
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<tr>
<td>Liver copper content: 388 mg Cu/g dry tissue*</td>
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<tr>
<td>DNA analysis of ATP7B: compound heterozygous state for the already described c.2532delA and c.3061-1 G&gt;A mutations</td>
<td>Liver Biopsy: diffuse parenchymal remodeling with a severe lobular disarray, nodular regeneration with hepatocyte ballooning, neocholangiolar proliferation, diffuse lymphocyte infiltrates with formation of nodular lymphocyte aggregates with T-cell phenotype, and plasma cell infiltrate</td>
<td>- Second follow up: Lab tests: Hb: 7.1 g/dL* Hct: 20.1 %* PLT: 36 x 10^9/L * PT: 83 s* 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*</td>
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<td>MRI: hepatocerebral degeneration</td>
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</tbody>
</table>

**Deutsch et al. (2013)**

<table>
<thead>
<tr>
<th>Greece</th>
<th>32 years old/ male</th>
<th>AH &amp; WD</th>
<th>Fatigue, low-grade fever and jaundice</th>
</tr>
</thead>
</table>

Physical exam: liver was slightly enlarged, painless, without tenderness on palpation, and with splenomegaly/ KF ring (+)

Lab tests: Normal blood count

Prednisolone 60 mg/day and Azathioprine 75 mg/day

- After three years, the patient is in good health and continu
<table>
<thead>
<tr>
<th>Santos et al. (2019) (6)</th>
<th>Brazil</th>
<th>25 Years Old/ Female</th>
<th>AIH to WD</th>
<th>Nausea, asthenia</th>
<th>Prednisone</th>
<th>8 weeks</th>
<th>-</th>
<th>AST: 72 U/L*</th>
<th>ALT: 69U/L*</th>
<th>ALP: 247U/L*</th>
<th>Alb: 2.30* g/dL</th>
<th>Bilirubin: 1.0 mg/dL</th>
<th>INR: 2.20</th>
<th>ANA: –</th>
<th>ASMA: –</th>
<th>Ceruloplasmin: 3.4 mg/Dl*</th>
<th>Urinary copper: 659 μg/24 hours*</th>
<th>GGT: 115 U/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR: 29 mm/1 h*</td>
<td>AST: 1219 IU/L*</td>
<td>ALT: 2327 IU/L*</td>
<td>γGT: 59 IU/L*</td>
<td>ALP: 172 IU/L*</td>
<td>TB: 29 mg/dL (direct: 24 mg/dL)*</td>
<td>Prothrombin time: 19 sec</td>
<td>INR: 2</td>
<td>Total proteins: 7.9 g/dL</td>
<td>Alb: 3 g/dL</td>
<td>Hepatitis markers (HBV, HAV, HCV): -</td>
<td>ANA: +</td>
<td>Serum Ceruloplasmin: 20 mg/dL</td>
<td>serum copper: 390 μg/Dl*</td>
<td>free copper: 315 μg/dL*</td>
<td>urine copper: 855 μg/24 h*</td>
<td>liver biopsy: interface hepatitis, portal invasion with mononuclear cell infiltrate and absence of fibrosis</td>
<td>Histochemical analysis with Rhodanine and Orcein: -</td>
<td>Molecular genetic analysis: -</td>
</tr>
</tbody>
</table>

**Notes:**
- * indicates significant values.
- D-penicillamine and interrupted prednisone treated on maintenance therapy with Prednisolone 2.5 mg/day and Azathioprine 75 mg/day.
<table>
<thead>
<tr>
<th>authors</th>
<th>Country</th>
<th>Age</th>
<th>Gender</th>
<th>Disease progression</th>
<th>Physical exam</th>
<th>Lab tests</th>
<th>Hepatitis markers</th>
<th>Imaging</th>
<th>Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zabolotsky et al. (2014)</td>
<td>Philadelphia</td>
<td>48 years old/ Female</td>
<td>AIH to WD</td>
<td>Abdominal pain and distention, and scleral icterus</td>
<td>Physical exam: scleral icterus</td>
<td>AST: 522 U/L* ALT: 510 U/L* TB: 10 mg/dl</td>
<td>Trans jugular hepatic biopsy: a pathological diagnosis of autoimmune hepatitis with liver parenchymal fibrosis and collapse</td>
<td>-</td>
<td>Orthotopic liver transplantation</td>
</tr>
<tr>
<td>Gromny et al. (2019)</td>
<td>Poland</td>
<td>30 years old/ Male</td>
<td>AIH to WD</td>
<td>-</td>
<td>Physical exam: KF ring (+)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Milkiewicz et al. (2000)</td>
<td>United Kingdom</td>
<td>15 years old/ female</td>
<td>AIH to WD</td>
<td>progressive lethargy, jaundice, skin rash and bilateral leg swelling, pruritus</td>
<td>Physical exam: young girl with cushingoid features including acne and abdominal striae, marks of excoriation, icterus, ascites and pedalo edema</td>
<td>AST: 103 U/L* ALP: 463 U/L* Bilirubin: 65 mmol/L* Alb: 22 g/L* INR: 2.2 IgG: 14 g/L</td>
<td>-</td>
<td>-</td>
<td>One month</td>
</tr>
</tbody>
</table>

*Studies on the explanted liver exhibited large quantities of copper, consistent with a diagnosis of WD

**without reject primary diagnosis**
<table>
<thead>
<tr>
<th>Author(s) et al. (Year)</th>
<th>Country</th>
<th>Age/Gender</th>
<th>Diagnosis Progression</th>
<th>Clinical &amp; Laboratory Findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milchewicz et al. (2000)</td>
<td>United Kingdom</td>
<td>24 years old/female</td>
<td>AIH to WD</td>
<td>PLT: 113x10^9/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</td>
<td>Steroid and AZT</td>
<td>of the prednisolone dose as her condition was improved</td>
</tr>
<tr>
<td>Naorniakowska et al. (2020)</td>
<td>Poland</td>
<td>13 years old/female</td>
<td>AIH to WD</td>
<td>general malaise, tiredness and right upper quadrant pain</td>
<td>AST: 165 U/L, ALP: 339 U/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</td>
<td>Two years advanced cushingoid features, icterus and ascites</td>
</tr>
<tr>
<td>Naorniakowska et al. (2020)</td>
<td>Poland</td>
<td>11 years old/male</td>
<td>AIH to WD</td>
<td>stomach pain</td>
<td>AST: 83 U/L, ALT: 123 U/L, GGTP: 69 U/L, Hepatitis markers (HBV, HAV, HCV): -, Liver Biopsy: steatohepatitis and fibrosis, ANA: +, Gammaglobulins: 14.98 g, IgG: 2824.5 mg</td>
<td>Glucocorticoids (GC’s) and AZT</td>
</tr>
<tr>
<td>Naorniakowska et al. (2020)</td>
<td>Poland</td>
<td>13 years old/male</td>
<td>AIH to WD</td>
<td>stomach pain and vomiting</td>
<td>AST: 313 U/L, ALT: 231 U/L, ASMA: 1: 640, Hepatitis markers (HBV, HAV, HCV): -, unconjugated hyperbilirubinemia US: hepatomegaly with portal hypertension, Severe inflammation,</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Last Name, First Name and Year (Page)</td>
<td>Country</td>
<td>Age</td>
<td>Gender</td>
<td>WD to AIH Conversion</td>
<td>Diagnosis</td>
<td>Liver Biopsy</td>
</tr>
<tr>
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<tr>
<td>Naorniako et al. (2020) (2)</td>
<td>Poland</td>
<td>5 years old/ female</td>
<td>-</td>
<td>AIH to WD</td>
<td>Severe fibrosis</td>
<td>AST: 125 U/l *</td>
</tr>
<tr>
<td>Dara et al. (2018) (21)</td>
<td>Iran</td>
<td>6 years old/ male</td>
<td>-</td>
<td>WD to AIH</td>
<td>Epistaxis, anorexia, weight loss</td>
<td>AST: 475 U/L*, ALT: 345 U/L*</td>
</tr>
<tr>
<td>Rezk et al. (2015) (23)</td>
<td>United States</td>
<td>19 year old/ male</td>
<td>-</td>
<td>WD to AIH</td>
<td>Fatigue, jaundice, dark urine, and pale stools</td>
<td>AST: 336 U/L*, ALT: 1002 U/L*</td>
</tr>
</tbody>
</table>

* Without reject primary diagnosis.
<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Laboratory Findings</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poland</td>
<td>15 years old/ female</td>
<td>WD to AIH</td>
<td>-</td>
<td>KF ring (+) ceruloplasmin: 16 mg/dl Urine copper: 4901 μg molecular investigation: 2 mutations</td>
<td>Penicillinamine -</td>
<td>Penicillamine was withdrawn. After the next 4 weeks, trientine was initiated, and penicillinamine 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.</td>
</tr>
</tbody>
</table>

**Abbreviations:** AIH: autoimmune hepatitis; WD: Wilson diseases; 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 ration; 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; and IgM: immunoglobulin M