THE SPECTRUM OF LIVER PRESENTATION IN WILSON'S DISEASE: A LITERATURE REVIEW

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Keywords: Wilson disease, liver presentation, acute liver failure, cirrhosis, acute Wilsonian hepatitis, chronic liver disease.

Introduction. Wilson's disease represents one of the genetic diseases that has lifelong treatment, which significantly improved the quality of life for patients and reduced the disabling complications associated with the lack of an early diagnosis.

Material and methods. A structured search was performed in PubMed and HINARI, using English search terms: "Wilson's disease", "acute liver failure", "cirrhosis", "acute Wilsonian hepatitis", "hepatic manifestation", "chronic liver disease", "asymptomatic Wilson's disease", and "active chronic hepatitis".

Results. Wilson's disease can occur at any age and can mimic the presence of other chronic liver diseases. The hepatic expression is highly variable, ranging from asymptomatic presentation to severe liver diseases, such as decompensated cirrhosis and acute liver failure. Any patient with transaminitis and abnormal parameters of cooper metabolism should be comprehensively and carefully evaluated to identify Wilson's disease early and to prevent misdiagnosis or unnecessary therapies. Confirmation of the diagnosis should not exclude the coexistence of other liver diseases.

Conclusions. The use of validated and adapted scores for Wilson's disease may facilitate diagnosis, but they cannot be used in acute liver failure. Considering that Wilson's disease presents itself with great phenotypic diversity and can evolve under the mask of other pathologies, it is necessary to carry out a careful differential diagnosis.

Cuvinte cheie: boala Wilson, prezentare hepatică, insuficiență hepatică acută, ciroză, hepatită acută Wilsoniană, hepatită cronică.

VARIETATEA FENOTIPULUI HEPATIC ÎN BOALA WILSON: REVIUL LITERATURII

Introducere. Boala Wilson reprezintă una din bolile genetice care la moment beneficiază de tratament pe tot parcursul vieții, ce îmbunătățește semnificativ calitatea vieții pacienților și reduce complicațiile invalidizante cauzate de întârzierea diagnosticului.

Material și metode. A fost efectuată o căutare structurată în PubMed și HINARI, folosind termenii în limba engleză: „Wilson's disease", „acute liver failure", „cirrhosis", „acute Wilsonian hepatitis", „hepatic manifestation", „chronic liver disease", „asymptomatic Wilson's disease", and „active chronic hepatitis".

Rezultate. Boala Wilson poate apărea la orice vârstă și poate imita alte boli hepatice cronice. Expresia hepatică este foarte fluctuantă, variind de la forma asimptomatică până la boli hepatice severe, cum ar fi ciroza decompensată și insuficiența hepatică acută. Orice pacient cu citoliză și parametri anormali ai metabolismului cuprului ar trebui să fie evaluat detaliat și atent pentru a identifica precoce boala Wilson și a preveni stabilirea unui diagnostic greșit sau terapii inutile. Confirmarea diagnosticului nu trebuie să excludă coexistența altor boli hepatice.

Concluzii. Utilizarea scorurilor validate și adaptate pentru boala Wilson poate facilita diagnosticul, dar acestea nu pot fi utilizate în insuficiența hepatică acută. Având în vedere că boala Wilson se prezintă cu o diversitate fenotipică mare și poate evolua sub masca altor patologii este necesar de efectuat un diagnostic diferențial atent.

ABBREVIATIONS: WD – Wilson's disease, **ATP7B** – ATPase copper transporting beta, **CLD** – chronic liver disease, **KFR** – Kayser-Fleischer ring, **HAI** – autoimmune hepatitis, **ACLF** – acute-on-chronic liver failure, **ALF-WD** – classic Wilsonian acute liver failure, **ALI** – acute liver injury, **ALT** – alanine aminotransferase, **AST** – aspartate aminotransferase, **LT** – liver transplantation, **EASL** – European Association for the Study of the Liver, **MELD** – a model for end-stage liver disease, **NAFLD** – nonalcoholic fatty liver disease, **PNPLA3** – patatin-like phospholipase domain-containing 3 genes.

INTRODUCTION

Wilson's disease (WD) was first described in 1912 by neurologist Samuel Kinnear Wilson as "progressive lenticular degeneration," a lethal family-transmitted neurological disease associated with chronic liver disease leading to cirrhosis (1). He noticed that "*the most curious and remarkable feature of this familial nervous disease is the constant presence of a profound degree of cirrhosis of the liver*", but he considered that "*This hepatic cirrhosis does not reveal itself by any symptoms during life*" (2). In his article, it was reported that one patient suffered from ascites, another died as a result of hematemesis, and two patients had episodes of jaundice before neurological manifestations, but at that time, hepatology was a lesser-known branch of medicine, and it was difficult to make a well-defined link between cirrhosis and its complications. Taking into consideration that the disease occurred in young people and most often in members of the same family, Samuel Wilson assumed several causes, such as toxins, and viruses, but was unable to confirm their implication (3).

WD, also known as hepatolenticular degeneration, is an autosomal recessive inherited disorder caused by the mutation in the ATPase copper transporting beta (ATP7B) gene that encodes ATP7B protein synthesis responsible for the incorporation of copper into apo-ceruloplasmin, as well as its biliary excretion. The occurrence of a pathogenic mutation in the Wilson gene causes the synthesis of a non-functional protein leading to a toxic accumulation of copper ions in various tissues, especially in the liver and brain (4).

WD is a disorder with multisystemic involvement characterized by an unpredictable clinical picture, and the time of appearance of clinical signs depends on the severity of organic lesions. Due to dysfunction in many systems, clinical and laboratory features are often subtle and can mimic alternative diagnoses, and in the process of evaluating a patient with a variety of signs, symptoms, and laboratory abnormalities it is necessary to make a differential diagnosis with WD (5). WD should be suspected in any person with altered liver parameters of unknown etiology or unidentified movement disorders or any patient with unexplained liver disease in association with neurological or neuropsychiatric disorders. Despite the clinical variety, the key features of WD are chronic liver disease (CLD), neuropsychiatric disorders, the presence of the Kayser-Fleischer ring (KFR), and episodes of acute haemolysis often associated with acute liver failure (ALF) (6).

WD is a potentially fatal disorder if not diagnosed early. Therefore, early recognition of symptoms and their confirmation by laboratory data, as well as the initiation of timely treatment are essential in preventing the progression of the disease and irreversible sequelae (7). Currently, WD is one of those rare genetic disorders that benefit from effective treatment throughout life, which has dramatically changed the prognosis of the disease and the quality of life in these patients (5).

The purpose of the study is to perform a literature analysis to recognize all variants of the liver phenotype in WD, identify chronic liver pathologies that can evolve with clinical, laboratory, and histological signs similar to WD, and highlight the distinctive features of the evolution of liver lesions in WD.

MATERIAL AND METHODS

An advanced search was performed in the PubMed and HINARI databases – the Research4Life program, using English search terms: *"Wilson's disease"*, *"acute liver failure"*, *"cirrhosis"*, *"acute Wilsonian hepatitis"*, *"hepatic manifestation"*, *"chronic liver disease"*, *"asymptomatic Wilson's disease"*, *"active chronic hepatitis"*. All publications offered by these platforms were selected, and articles in English were prioritized, although no language limits were set. Articles published in the Republic of Moldova and Romania are also included. A preliminary analysis of the titles was performed and selected original articles, narrati-

ve syntheses, meta-analyses, systematic reviews, series of cases relevant to the research topic, book chapters, which addressed CLD, a hepatic manifestation of WD, concomitant disease in WD, diagnostic criteria and clinical approach of WD patients.

RESULTS

According to the search criteria and after analyzing the information from the HINARI and PubMed databases, 50 relevant sources were chosen with representative content for this literary review. Articles with content not relevant to the topic, as well as those not available for free viewing through the HINARI database were excluded from the search list.

Epidemiological data

Wilson's disease is found worldwide. The reported prevalence is traditionally 1:30,000 people (6), although research by Coffey and colleagues (8) has shown a genetic prevalence of more than 1: 7026 people, in socio-culturally isolated communities (9) as well as in populations with a high risk of inbreeding (10) was observed a very high prevalence. The mismatch between clinical and genetic prevalence can be explained by the presence of several potential factors that can influence it: incomplete genetic penetration, failed diagnosis, and epigenetic and metabolic factors (11). WD has high phenotypic variability, and research that has studied genotype-phenotype correlations has had contradictory results (12). Although the genetic aspects of the disease have been elucidated, the interaction of epigenetic, metabolic, and habit factors (diet, traditions, exposure to toxic environment) may contribute to clinical diversity (13). Hepatic impairment is present in 40-50% of patients (14), although data ranging from 18-84% at the time of primary diagnosis have been reported (15, 16). In the study conducted by Ferenci P. et al. (12) on 1357 patients (children and adults; index patients and siblings), they observed that in index patients, the hepatic presentation was present in 61% and more frequently in women. The difference in data could be explained by the predominant symptomatic manifestations presented by the patient and the specialist to whom he was referred for primary evaluation (ex. the neurologist reports only neurological impairments), and the present untreated asymptomatic forms manifest

themselves as the disease progresses being described late, in the stage of complications.

Age at onset of symptoms

The age of onset depends on the type of mutation and the degree of impairment of ATP7B protein function, mutations in functionally important regions are associated with severe evolution, early onset, and a predominant hepatic presentation, while mutations in less important regions of the gene are associated with late-onset and a predominant neurological or psychiatric presentation (7). WD can occur at any age, but primary hepatic presentations are most commonly diagnosed between the ages of 5-35 although may occur earlier or later (6). It is most frequently found in adolescence, but some cases of hepatic pattern have been reported in very young children (<5 years old) (17-21). The diversity of liver disease in these very young children with WD is remarkable because they can present any clinical pattern from asymptomatic to severe disease. Some children are diagnosed with WD when they have had an intercurrent health problem (22), while others are detected by family screening (12). Analyzing the data from the French Wilson's disease registry, which contained 604 patients, it was observed that 51.6% of patients at the time of diagnosis were up to 16 years old; 47% had liver damage, 32.2% had a neurological phenotype and 20.8% were identified in family screening (22).

Clinical evolution

The disease expression is highly variable, ranging from asymptomatic subjects to patients with severe liver disease (11). The symptomatic variant presents hepatic, neurological, or mixed phenotype, considering that the liver and brain injury predominates, but other organs such as the heart, kidneys, osteoarticular system, endocrine glands, genitals, and skin may also be involved. The silent variant (without any symptoms: apparently well) includes those patients conventionally described as asymptomatic or presymptomatic (it assumes that the disease will become clinically manifest), being identified through family or occasional screening, following a routine evaluation, or intercurrent diseases (13).

Hepatic manifestations often occur with a nonspecific picture for a long time and precede the onset of neurological symptoms by as much as 10

years. They are characterized by a wide clinical variety: asymptomatic form (increased transaminases, isolated hepatomegaly and/or splenomegaly), CLD (hepatitis or cirrhosis), and ALF. Some clinical features are found in all types of hepatic presentations, which should raise suspicion for WD. A research on a group of 55 patients in Romania, highlighted that 25.4% of patients had the asymptomatic disease, 52.8% had CLD and 21.8% had ALF (23). The research in our country revealed that the average age at diagnosis was 20.0±1.25 years (the interval being between 9-38 years); the duration of establishing the diagnosis varies from 6 to 36 months; 52.5% of patients had liver damage as an initial clinical symptom, and in 72.5% of patient's liver manifestations such as liver cirrhosis, steatosis, hepatomegaly, hepatic failure was determined (24).

Most patients with neurological symptoms will have some degree of liver damage at presentation. The duration from the onset of symptoms to diagnosis is two to three times longer in patients with a neurological phenotype than in those with liver damage (44.4 months versus 14.4 months) (25), which denotes that neurological symptoms may be subtle and easily missed by patient and specialist, as well as the rapidly progressive evolution of the disease in patients with hepatic manifestations leads to initiate paraclinical evaluation with the identification of WD specific changes.

A working group of the 8th International Meeting on Wilson disease and Menkes disease in Leipzig/Germany (April 2001) agreed to classify symptomatic patients corresponding to the organ predominantly involved in their presented symptoms (tab. 1). They also proposed a scoring system for the diagnosis of WD, which is an important tool in examining a patient suspected of WD and includes clinical, haematological, biochemical, histological and genetic data; a score ≥4 points may establish the diagnosis (26). This classification can help to assign patients to the appropriate group, but a score <4 guides clinicians on which tests are needed to establish and put the final diagnosis.

Table 1. Phenotypic classification of Wilson's disease (26).

Hepatic presentation (H) – requires the exclusion of neurological symptoms by performing a detailed neurological clinical examination at the time of diagnosis.		
H1	Acute hepatic WD	Acute onset of jaundice in previously apparently healthy subjects, either due to hepatitis-like illness or Coombs-negative haemolytic anaemia or a combination of both. May progress to ALF requiring emergency liver transplantation.
H2	Chronic hepatic WD	Any manifestation of CLD, with or without symptoms. It may progress to or even present as decompensated cirrhosis. The diagnosis is based on standard assessments: biochemical and/or radiological or liver biopsy.
Neurologic presentation (N) – patients with neurological and/or psychiatric symptoms present at the time of diagnosis.		
N1	Associated with symptomatic liver disease.	Patients usually have cirrhosis of the liver at the time of diagnosis of neurological WD. CLD may precede the onset of neurological symptoms for several years or may be diagnosed during the diagnostic work-up of the patient with neurological symptoms.
N2	Not associated with symptomatic liver disease.	Documentation of the absence of marked liver disease (steatosis/fibrosis may be present at any time) requires a liver biopsy.
Nx	The presence or absence of liver disease is not investigated.	
Other (O)		

Acute hepatic presentation

Acute-WD predominantly affects children or young adults and may develop as acute non-viral hepatitis, acute-on-chronic liver failure (ACLF), or ALF. The common symptoms in children are frequently nonspecific, ranging from fatigue, anorexia, nausea, vomiting, and weight loss to abdominal pain and jaundice. Jaundice is typically more by decompensation CLD or due to intravas-cular haemolysis associated with classic Wilsonian acute liver failure (ALF-WD) (25, 26). Wilsonian acute hepatitis is more common in women with a female-to-male ratio 2:1 ratio in some series and even higher in others, possibly due to hormonal factors (27).

Acute liver injury (ALI) is a condition when the patients develop coagulopathy, without any alte-

ration of consciousness, while ALF describes the subjects who develop both coagulopathy and altered mentation (28). Dhawan and colleagues (29) reported that 2 of 15 patients that died had ALI which emphasizes the need to identify a patient at an early stage without encephalopathy and to initiate procedures for liver transplantation (LT). A rapid worsening of ALI can lead to ALF related to Wilson's disease that manifests as ALF-WD, and ALF without a classic profile. ALF-WD is characterized by jaundice, moderate to severe Coombs-negative haemolytic anaemia, low serum alkaline phosphatase, mild to moderately elevated serum aminotransferases, coagulopathy, hepatic encephalopathy, rapidly progressive renal dysfunction (acute tubular injury with renal failure). ALF without a classic profile includes jaundice, coagulopathy, and hepatic encephalopathy; such an evolution does not exclude WD etiology. ACLF can be noted in cases with pre-existing advanced liver damage and can be induced by intercurrent infections, hypotension, discontinued WD therapy against medical advice, or acute worsening of WD. Any type of ALF is a medical emergency and it is essential to differentiate them because the algorithm for care and treatment differs (6, 22, 28). ALF due to WD represents about 6-12% of all cases referred to urgent LT and often is the only therapy option (6).

ALF was classified by O'Grady et al. (30) into 3 groups: hyperacute (1-7 days), acute (8-28 days), and subacute (5-12 weeks), being differentiated by the time when hepatic encephalopathy occurred concerning the onset of symptoms (usually jaundice), although the European Association for the Study of the Liver (EASL) guidelines summarize other classifications as well (31). The hyperacute and acute phases are usually easy to diagnose due to obvious clinical and paraclinical changes, while the subacute phase can be confused with decompensated cirrhosis, losing the opportunity to do LT. Acute hepatic presentation is a special condition accepted by EASL guidelines as having ALF if they develop hepatic encephalopathy even if an underlying CLD is present (31).

The values of copper metabolism parameters are accurate indicators in WD but are less relevant in ALF. Being an acute-phase protein, ceruloplasmin can be normal or elevated, total serum copper and urinary copper in 24 h are increased due to massive liver necrosis with the release of copper in the blood (32). However, urinary copper excre-

tion is statistically significantly higher in WD patients compared to ALF from other causes, while the values of ceruloplasmin and total copper did not show a statistical difference (33, 34).

Several indicators have been proposed to differentiate ALF due to WD from other causes. Alkaline phosphatase and alanine aminotransferase (ALT) have been observed frequently in these patients, respectively, a ratio of alkaline phosphatase to total bilirubin <2.0 and aspartate aminotransferase (AST) to ALT>4.0 was identified to recognize the ALF due to WD, but comparative studies did not show significant differences between groups (ALF due to WD and other causes) (33, 34). However, WD patients present clinically significant low levels of haemoglobin, transaminases, and cholinesterase, the latter being explained by the pre-existence of CLD with significant functional lesions and advanced hepatopriv syndrome (34).

ALF can cause significant diagnostic difficulties due to useless information from the diagnostic criteria of the WD, in a critical time window, and the lack of sensitive and specific criteria for the rapid diagnosis. The New Wilson's index, a model for end-stage liver disease (MELD), and the Child-Pugh score are useful tools to make decisions about LT; however, none of them is an independent decisive tool (33). The New Wilson Index predicts mortality without LT, using serum bilirubin, international normalized ratio, AST, albumin, and white cell count; a score ≥11 points is fatal without LT (29), while a Child-Pugh score ≥7 points can show the need to include the patient in the waiting list for LT (33).

The mortality rate in ALF due to WD is around 100% if LT is not performed urgently. This phase is associated with poliorgan failure which aggravates the patient's condition. It is essential to differentiate ALF due to WD from other causes because awaiting LT one of the goals of therapy is to reduce acute injury caused by the massive release of toxic copper (33, 34). The procedures for rapidly decreasing the amount of copper are known as bridging techniques for LT and include: therapeutic plasma exchange, albumin dialysis, plasmapheresis, hemofiltration, fractioned plasma separation and absorption, liver dialysis with single-pass albumin dialysis, early institution of renal replacement therapy, and molecular adsorbents recirculating system. They stabilize the patient and improve biochemical parameters to pass LT successfully (35).

Chronic hepatitis

A clinically important presentation is chronic active hepatitis that can evolve under the mask of nonalcoholic fatty liver disease (NAFLD) or autoimmune hepatitis (HAI) (30). Being characterized by an active inflammatory process, it can progress over time to advanced fibrosis with a negative impact on the patient's prognosis. Clinical evolution is difficult to distinguish from that observed in chronic hepatitis of other causes, and nonspecific biochemical results associated with borderline changes in copper metabolism may lead to a delayed diagnosis (6, 13).

Histological examination in WD is polymorphic and nonspecific, and only the correlation of clinical and paraclinical data guarantees a correct diagnosis (36). As a result of the mutation, copper is not eliminated by the bile and accumulates in toxic amounts in the liver. That affects the function of mitochondria and causes beta-oxidation of fatty acids, leading to steatosis. The hepatocyte contains fat droplets of different sizes from macro- to microvesicles and the histological picture changes with the progression of the disease. In the initial phase, macrovesicular steatosis is observed. With the progression of the disease morphological features of either steatohepatitis or chronic active hepatitis can be determined. Later the histological appearance acquires similarities with chronic active hepatitis of autoimmune or viral type, and finally, cirrhosis can be detected (25, 37).

Nonalcoholic fatty liver disease and WD

Whereas obesity is a global epidemic, clinicians must take into account that all patients suggestive of steatohepatitis, regardless of age and weight, need to be evaluated for WD before starting treatment. Comparative studies (NAFLD due to WD versus metabolic NAFLD) have shown that the severity of hepatic steatosis increases with the amount of copper in the liver tissue, respectively hepatic steatosis in WD is not induced by the associated metabolic conditions, but directly by the accumulation of copper. However, the pathogenesis of NAFLD due to WD is a multifactorial one, and the involvement of metabolic conditions as cofactors in this process is not excluded (37). A recent study on 98 Caucasian WD patients, highlighted the involvement of the G allele of the genetic polymorphism in rs738409 in the patatin-like phospholipase domain-containing 3 genes (PNPLA3) in the development of NAFLD associated with WD, as independent predictors of moderate to high-grade steatosis (38).

Autoimmune hepatitis and WD

Some WD patients may summarize diagnostic criteria for HAI type 1, such as cytolyzes, positive anti-nuclear antibody and/or smooth muscle antibody, and histologically compatible findings on liver biopsy, but compared to patients with HAI, the response to corticosteroid treatment is poor. The appearance of autoantibodies is not known, possibly as a consequence of hepatocyte necrosis or as a concomitant disease, but such an association usually delays the diagnosis of WD. The coexistence of WD and HAI is rare, but, if necessary, the combined therapy of prednisolone and d-penicillamine is recommended (39, 40, 41).

Cholestatic liver diseases and WD

Differential diagnosis between WD and cholestatic liver diseases represents a real challenge in clinical practice due to clinical and laboratory similarities. It is known that cholestatic syndrome, especially primary sclerosing cholangitis, can occur with secondary systemic copper accumulation associated with changes in copper metabolism parameters. It is important to note that in WD, the level of ceruloplasmin is significantly reduced compared to cholestatic cases (6 vs. 16 mg/dL), the 24-hour urinary copper is increased much more (322.3 vs. 74.5 µg/day) and after the initiation of therapy with chelators, a decrease in liver copper content is observed and the level of ceruloplasmin may decrease more (42).

Cirrhosis

The progression of liver fibrosis leads to the installation of liver cirrhosis which is initially compensated, but with the aggravation of portal hypertension, there is decompensation of cirrhosis associated with classic complications such as ascites, encephalopathy, and haemorrhage from esophageal varices. The evolution of cirrhosis in WD is no different than other etiologies being present fatigue, confusion due to hepatic encephalopathy, spider angiomas, gynecomastia, palmar erythema, bruising, bleeding, and muscle wasting (43). Therefore, patients with advanced CLD need to be screened periodically for signs of portal hypertension (esophageal varices and splenomegaly) (43), but also liver neoplastic processes (44).

Decompensated cirrhosis increases the risk of bacterial infections or sepsis, as well as spontaneous bacterial peritonitis. Hepatic encephalopathy, hepatorenal syndrome, acute kidney injury, hepato-pulmonary syndrome, porto-pulmonary hypertension, cirrhotic cardiomyopathy, and relative adrenal insufficiency are complications associated with a high degree of mortality (30, 43).

In a large Austrian cohort that included 229 patients, delay in diagnosis was observed to reduce survival time, and the presence of cirrhosis at the time of diagnosis was the lead predictor of mortality. It should also be highlighted that cirrhosis was present in 47% of cases (66/140 patients) with the hepatic presentation, in 34% of cases (21/61 patients) with the neurological presentation, and in 9% of cases (2/23 patients) in asymptomatic patients (45).

Hepatobiliary malignancies and WD

Although the occurrence of liver neoplasia is a frequent event in CLD, the association of tumors with WD is rare, and the risk of development is not clearly defined, even in cirrhotic patients (44). Toxic accumulation of copper might be expected to be associated with the induction of carcinogenesis, but high copper content in the liver has been hypothesized to have a protective effect, although studies are conflicting (46). A European multicenter cohort study that included 1186 patients with WD identified 8 cases with hepatocellular carcinomas and 6 cases with intrahepatic cholangiocellular carcinomas and found that the prevalence of liver neoplasia in WD was 1.2% and the incidence was 0.28 per 1000 person-years (44). A Dutch retrospective cohort study found that the annual incidence of hepatocellular carcinoma in WD is 0.09% in all patients and 0.14% in those with cirrhosis, therefore dynamic cancer surveillance in WD patients is not recommended, unless there are additional risk factors (e.g., hepatitis B or C, alcohol) (47).

Asymptomatic presentation

Most asymptomatic patients are identified through family screening, which is performed in stages, initially evaluating siblings, then first-degree relatives (and not just first-degree ones). This allows the initiation of treatment as early as possible, preventing the progression of the disease and the appearance of irreversible sequelae

(48). Currently, many patients are detected in the asymptomatic phase due to the awareness of this disease in clinical practice and the routine performance of liver function tests (23). No clinical signs or symptoms of manifest liver disease may be observed in these patients, sometimes isolated mild hepatomegaly and/or splenomegaly may be their only findings on physical examination, but they may have some abnormalities of liver tests as mild persistent elevations of ALT or AST (48). Up to 11% of asymptomatic patients had advanced CLD not previously diagnosed (49).

Asymptomatic patients are a real challenge in diagnosing WD, as they may present asymptomatic liver test changes, but with normal values of some of the copper metabolism tests, which reduces the accuracy of the Leipzig score. The diagnosis of WD in asymptomatic patients with minimal changes in copper metabolism or overweight/obese patients with hepatic steatosis should be re-evaluated by histological examination and genetic testing, to exclude a mild phenotype or a modifier gene intervention that regulates copper metabolism in the presence of malfunctioning ATP7B protein (36).

DISCUSSIONS

Any patient presenting increased transaminases needs to be considered for clinical work-up similarly to any other acute/chronic hepatitis and cirrhosis, as the usual histological examination is not pathognomonic (6). The differential diagnosis should be done between WD and viral hepatitis (B, C, D), HAI, cholestatic syndromes, drug-induced liver injury, nonalcoholic or alcoholic steatohepatitis, hemochromatosis, alpha-1-antitrypsin deficiency, ischemic liver damage, and indeterminate causes. In the case of the patient suspected of WD, attention will be paid to the physical examination to identify the stigmas characteristic of liver disease and subtle extrahepatic manifestations, history of unexplained episodes of jaundice or hemolysis, unexplained liver disease with or without neurological or neuropsychiatric disorders in family members (siblings, parents, grandparents, aunt, uncle), current alcohol consumption (a presence of alcohol withdrawal), recent administration of hepatotoxic drugs, unexplained amenorrhea or delayed puberty (30, 50). No single test is specific for diagnosis, but a range of tests must be applied. Given that the parame-

ters of copper metabolism can be influenced by many conditions (e.g., acute inflammation, hyperestrogenemia, increased zinc uptake, healthy heterozygotes, chronic cholestasis, etc.), the diagnosis of copper findings can only be interpreted plausibly in the context of other findings (clinical, laboratory and genetic) to avoid false-positive or false-negative results (32). Ferenci P. and colleagues (12) reported that 3-10% of patients present a normal histological appearance or mild changes, therefore when performing a liver biopsy, it is necessary to do liver copper quantification. To make a differential diagnosis, it is recommended to perform an imaging examination: abdominal ultrasonography, magnetic resonance, or computed tomography, and in the advanced stages, it is important to evaluate the degree of liver fibrosis by transient elastography and biochemical scores of fibrosis (25, 27). The KFR is seen in 45-50% of patients with liver damage and 95% of neurological damage (6).

The presence of WD does not exclude other liver pathologies and vice versa. Reduced vigilance in special clinical cases can lead to several situations. First, the simultaneous presence of another disease may delay the diagnosis of WD, with progressive liver damage. Second, targeted untreated concomitant liver disease can lead to the worsening of lesions despite adequate treatment with chelators for WD. Third, the patient with WD may have overdosed with chelating agents developing secondary copper deficiency and various side effects, while the concomitant disease remains unrecognized (1, 13, 50).

CONCLUSIONS

1. The evolution of liver lesions in WD can be very variable, ranging from an asymptomatic state to decompensated cirrhosis, accompanied by its classic complications, therefore establishing the diagnosis in the early stages can prevent the occurrence of irreversible sequelae.

2. The examination of the patient with changes in liver function tests should be extensive and objective, using validated scores and carefully analyzing the results of investigations.

3. Acute liver failure due to WD is rather difficult to differentiate from other etiologies due to the lack of sensitive and specific criteria for diagnosis in this type of presentation, which complicates potential decisions regarding the type of treatment required.

4. Confirmation of the diagnosis should not exclude the co-existence of other liver diseases, and the complex and systematic approach of the patient prevents delayed diagnosis, irreversible injury with organ failure, and administration of ineffective therapies.

CONFLICT OF INTERESTS

None to declare.

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