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MEETING REPORT

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# Pitfalls in the management of metabolic liver diseases (debate)

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## Abstract

**Background** The liver has an important role in the different metabolic processes. So, inborn errors of metabolism will result in several metabolic disorders, which can cause acute or chronic liver disease leading to cirrhosis and liver cancer.

**Main body** In one of our Egyptian conferences, the United Conference of Hepatogastroenterology and Infectious Diseases (UCHID) 2022, our authors discussed the debates on the management of Wilson's disease, hereditary hemochromatosis, and alpha one anti-trypsin deficiency.

**Conclusion** The session summarized the pitfalls in the management of the 3 serious metabolic liver disorders with focused take-home messages to every physician.

**Keywords** Metabolic liver disease, Wilson's disease, Hemochromatosis, Alpha-one anti-trypsin deficiency, Pitfalls

## Background

The liver plays a critical role in several metabolic pathways involving carbohydrates, protein, lipids, and other elements. Thus, inborn errors of metabolism will lead to various abnormalities which may manifest as serious acute illness or as a chronic liver disease with progression to cirrhosis, liver failure, and HCC [1].

In one of our scientific Egyptian meetings, the United Conference of Hepatogastroenterology and Infectious Diseases (UCHID) 2022 provided an optimum opportunity of sharing medical experiences, with the gathering of expert medical staff members along different governates of the country to present fruitful enriched sessions/lectures/workshops/open discussions. Our session entitled "Pitfalls In The Management Of Metabolic Liver Diseases (debate)" discussed the journey from suspicion to diagnosis to treatment "debates" in Wilson's disease, hereditary hemochromatosis, and alpha one anti-trypsin deficiency in form of answered questions.

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## Main text

### Wilson's disease (WD)

#### *Does Wilson's disease (WD) represent a rare entity?*

It is an autosomal recessive rare disorder with a prevalence of one in 10,000–30,000 (1 in 90 carry a mutation), caused by ATP7B, encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper within hepatocytes to control copper Cu metabolism regulation, and so, the ATP7B gene mutation results in excessive copper Cu deposition (liver, brain, and eye); Wilson's

disease (WD) usually begins at 5 to 35 years old. The diagnosis relies on both clinical and laboratory findings. Fortunately, it is a treatable disorder so earlier diagnosis and treatment are a must [2, 3].

### *Is Wilson's disease (WD) diagnosis considered to be a challenge?*

It is known that no gold standard for Wilson's disease (WD) diagnosis; furthermore, several obstacles hinder the diagnosis: diagnostic errors by referring doctors from different specialties as illustrated in Table 1, isolated laboratory findings at presentation (thrombocytopenia, hemolytic anemia), copper tests' false interpretation, atypical radiological findings, non-specific pathology, genetic testings' (600 mutations) unavailability and costs, and finally no single confirmatory diagnostic test (mainly relies on scores/algorithmic approaches) [4, 5].

### *Are the different diagnostic algorithms sufficient for Wilson's disease (WD) diagnosis?*

The clinical practice guidelines have relied mainly on case series and expert consensus rather than the randomized trial data to supplement the available limited data as shown in Fig. 1 [6–8].

### *What is the role of genetic testing in Wilson's disease (WD)?*

The concept of genetic testing's indications for Wilson's disease (WD) diagnosis has been misunderstood in practice. It is useful in a family screening for the first-degree relative mutation analysis of a Wilson's disease (WD) patient or haplotype studies as illustrated in Fig. 2 [7, 9].

**Table 1** Lists of different clinical manifestations of WD

| Clinical Manifestations of Wilson's Disease | |
|---|---|
| Hepatic | Asymptomatic hepatomegaly, elevated transaminases, acute/chronic hepatitis, cirrhosis, ALF, fatty liver |
| Neuro-psychiatric | I. Akinetic-rigid syndrome as Parkinsonism<br>II. Pseudosclerosis is dominated by tremors<br>III. Ataxia<br>*Diagnostic errors by referring doctors from different specialities*<br>V. Psychiatric symptoms as behavioural changes, deteriorating school performance, depression, anxiety, psychosis |
| Skeletal | Arthralgia, arthritis, osteoporosis, osteomalacia, chondromalacia |
| Haematological | Hemolytic anemia, thrombocytopenia, pancytopenia |
| Ocular | Kayser-Fleischer rings, sunflower cataracts |
| Renal | Renal stones, renal tubular acidosis, Fanconi syndrome |

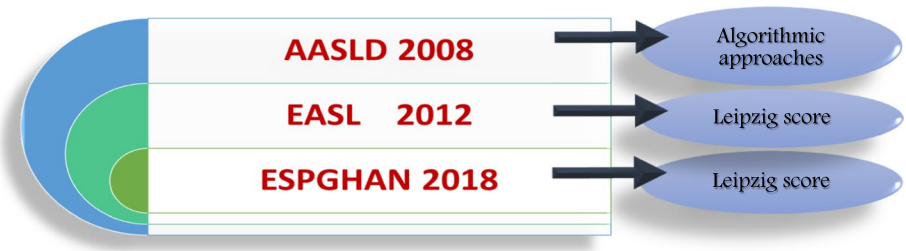


**Fig. 1** The most accepted algorithmic/scoring approaches for WD diagnosis

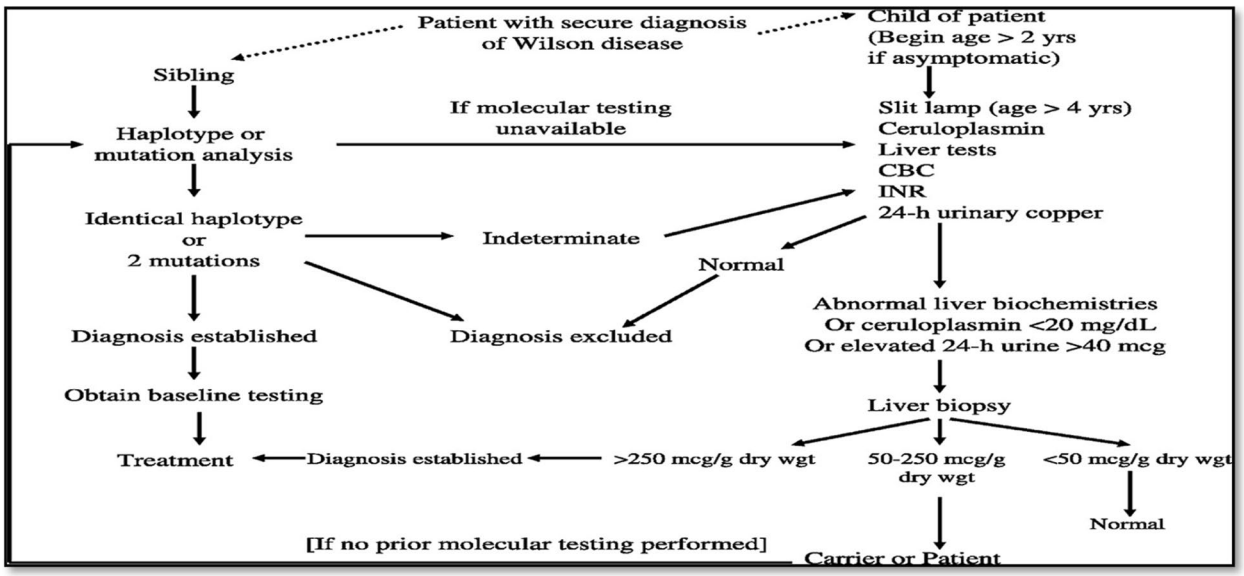


**Fig. 2** Screening for Wilson disease in a sibling/child of diseased WD patient

***What about the difficulties we face in the treatment of Wilson's disease (WD)?***

Although it is a treatable disorder, there are obstacles in the management that the physicians face including the diet, the use of single Vs dual chelating agents (no consensus), reaching optimal hepatic drug effect (6–12 months), the disease complications vs drug side effects (renal, neurological, blood elements) which represent a challenge in both diagnosis and management, introduction of gene therapy (ongoing trials), and finally the management of the special situations as seen in Table 2 [4–10].

***When is it indicated to go for liver transplantation in Wilson's disease (WD) patient?***

Till now medical treatment (chelators, zinc (ZN), tetra-thiomolybdate MTTM) is effective in most cases of hepatic Wilson's disease (WD). However, liver

**Table 2** Management protocol of WD in the most widely used clinical practice guidelines

| | AASLD2008 | EASL2012 | ESPGHAN2018 |
|---|---|---|---|
| Symptomatic<br>Initial phase | a) Chelating agent<br>b) Zn<br>(decompensated cirrhosis) | a) Chelating agent<br>b) Zn<br>(neurological) | a) Chelating agent<br>b) Zn<br>(decompensated cirrhosis) |
| Maintenance phase | Chelating Agent or Zn | Chelating Agent or Zn | Zinc |
| Asymptomatic | Chelating Agent or Zn | Chelating Agent or Zn | Zinc |

Special situations

| | AASLD2008 | EASL2012 | ESPGHAN 2018 |
|---|---|---|---|
| Pregnant | Chelating agent ↓ dose Zn | Chelating agent ↓ dose Zn | Chelating agent ↓ dose Zn |
| Lactating | D-penicillamine avoided | D-penicillamine avoided | D-penicillamine avoided |
| Surgery | Chelating agent ↓ dose | — | — |
| HCC/ICC screening | Not recommended | — | — |

transplantation should be considered in fulminant hepatitis and progression of liver disease (decompensation) despite compliance with medical treatment [6, 7].

#### *How should we suspect fulminant Wilson's disease?*

Although it is difficult to differentiate from other causes of fulminant hepatic failure FHF, it is important for every physician to consider; clues are low alkaline phosphatase with evidence of negative Coombs' test intravascular hemolysis and modest ALT/AST elevation (AST > ALT). A hint to know: acute decompensated children with Wilson's disease WD is not a well-defined entity and may not have the full picture of fulminant hepatic failure/acute liver failure, and so Wilson's index (Wilson's disease WD prognostic score) that had been designed for predicting mortality without transplantation should be addressed well. It is based on serum total bilirubin, international normalized ratio (INR), aspartate aminotransferase (AST), white blood cell count (WBC), and albumin, with a score of $\geq$ 11 were predicted to need transplantation [11–14].

#### *Does the presence of neurological symptoms contraindicate liver transplantation in Wilson's disease?*

It is controversial as it relies mainly on the symptoms' degree and duration. In a systematic review literature of 48 articles reporting the outcomes in 302 pts as the following, 71% has major improvement and 7% showed no difference after liver transplantation LT, while 8% developed neurologic worsening and death of around 9% [15, 16].

### Hereditary hemochromatosis (H.H)

#### *Does the diagnosis of hereditary hemochromatosis (H.H) considered to be under/overestimated?*

It is considered the commonest European genetic disorder, ranging from one in 100–300 and less common among African population with six times higher in Whites than in Blacks. Hereditary hemochromatosis (H.H) is underdiagnosed in the general population but over-diagnosed in patients with secondary iron overload. The diagnosis can be mysterious and rare because of the nonspecific nature of the symptoms and the incomplete penetrance of the genotype [17].

#### *Is hereditary hemochromatosis (H.H) an adult or young onset-related disorder?*

Hereditary hemochromatosis (H.H) usually becomes evident after the age of 40 in males (median age, 51 years), while in females, it occurs later after the age of 50 (median age, 66 years) because the menstruation causes physiologic blood loss that increases iron removal. However, in juvenile hemochromatosis, which is unrelated to HFE mutations, symptoms appear at the age of 10–30. Furthermore, neonatal hemochromatosis NH which is a misnomer and instead is termed "neonatal iron overload" is a fatal disease in which severe liver disease in the newborn is accompanied by extrahepatic siderosis that rapidly deteriorates shortly after birth up to death. Gestational alloimmune liver disease (GALD) has been observed to be the cause of fetal liver injury in most of the neonatal hemochromatosis cases. However, so far the cause of such injury remained a mystery [18, 19].

#### *What is the relation between gene mutations and different types of hereditary hemochromatosis (H.H)?*

It is a little bit confusing so to simplify. At least 5 different genes HFE, HJV, TFR2, SLC40A1, and HAMP mutations in H.H are involved in hepcidin production/activity. The HFE gene is considered the most recognized one, and it is located on chromosome six within the HLA class I region. The two mutations of the HFE gene (C282Y and H63D) are responsible for most of the hereditary hemochromatosis (H.H) cases. A hint to know, late-onset moderate iron overload is related to BMP6, which affects hepcidin gene transcription upregulation [17–20].

As regards the relation between genes and HFE-related H.H types, type 1 HFE1 is the result of the C282Y and H63D mutations and is located at band 6p22. Type 2 (gene HFE2) is known as the Juvenile hemochromatosis (JH) and is mapped to band 1q21. Type 3 HFE3 (adult form of hemochromatosis) results from transferrin receptor 2 gene TfR2 mutations and is located on band 7q22. A hint to know, the gene encoding Ferroportin (SLC11A3) is not linked to HFE; instead, it was related to autosomal dominant AD hemochromatosis and characterized by earlier precipitation of iron (Fe) in the reticuloendothelial cells. Finally, the different hereditary hemochromatosis (H.H) types could have the same clinical presentations [17–20].

#### *When shall we order genetic testing for the diagnosis of hereditary hemochromatosis (H.H)?*

Most studies reported that both phenotypic and genotypic criteria are essential for the diagnosis of hemochromatosis. It is known that the typical hemochromatosis patient has a pair of the C282Y mutation of the HFE gene known as C282Y homozygote with evident abnormal iron lab profile. On the contrary, the heterozygotes C282Y/H63D and H63D homozygotes commonly have a normal lab. Hereditary hemochromatosis (H.H) genetic

testing is indicated in the first-degree relatives, patients with abnormal iron overload lab findings, and known liver disease patients with evidence of abnormal iron profile, even if other causes of liver disease coexist [17–21].

### Alpha one anti-trypsin deficiency (A1ATD)

#### *Is alpha one anti-trypsin deficiency (A1ATD) considered to be a rare disease?*

It is an uncommon disease but not a rare one. It is one of the three most common lethal genetic disorders among whites (the other two are cystic fibrosis and Down syndrome). The responsible genetic defect affects one in 3000–5000 populations in all ethnic groups; however, A1ATD is most prevalent in Europe (Scandinavia, Spain, and Portugal) and North America, and A1ATD has been reported virtually in all racial subgroups studied in almost 70 countries in 11 geographical regions around the world [22]. It is underdiagnosed for many reasons, not every patient with alpha one anti-trypsin deficiency (A1ATD) develops the disease, and if so, mostly not clinically significant, the deficient enzyme is congenital with a bimodal distribution regarding symptoms and the liver disease incidence increases with age [21, 23–26].

#### *Why alpha one anti-trypsin deficiency (A1ATD) is usually underdiagnosed?*

Early diagnosis is sporadic, and the patient is usually diagnosed at a median age of 45.5 ± 9.5 years with only around 15% of patients have been diagnosed. Unfortunately, the diagnosis is often missed for many reasons (especially mild-moderate degrees); Limited physician awareness regarding alpha one anti-trypsin deficiency (A1ATD) as well as no strict clear screening guidelines to adhere/follow for those with symptoms, the presentation resembles other more common disorders rather than alpha one anti-trypsin deficiency (A1ATD) to consider/suspect such as asthma, COPD, or chronic cough (1–5% of COPD patients are estimated to have alpha one anti-trypsin deficiency). Furthermore, the presentation in the affected liver disease patients is usually not specific to alpha one anti-trypsin deficiency (A1ATD) and the exact cause may remain unexplained; not even a single physical sign could confirm the diagnosis [21, 23].

#### *What is the role of genetic heterogeneity in disease presentation/management?*

It is known that the disease presentation relies on the type of mutation. Over 100 phenotypic alpha one anti-trypsin deficiency (A1ATD) variants have been detected, but only one phenotype Pi (the serious form is 2 "Z" copies) Pizz is responsible for almost all case presentation in the form of emphysema and liver disease, and Pisz and Piz/Null have also been linked to the disease presentation to a lesser degree, while PiNull/Null carriers are only presented with emphysema. On the contrary, PiMZ carriers are usually asymptomatic with a slight increase risk of developing the disease. A hint to know, heterozygosity in the Z gene, including ZNull/MZ mutation, is at risk for developing cirrhosis if coexists with other risk factors such as alcohol abuse or HCV infection [24, 25].

#### *Are the available diagnostic tools for alpha one anti-trypsin deficiency (A1ATD) satisfactory?*

Every physician should be aware that accomplishing the definitive diagnosis for alpha one anti-trypsin deficiency (A1ATD) depends mainly on both biochemical and/or genetic tests. The gold standard for the diagnosis is the A1AT phenotype, while serum A1AT levels are beneficial in the disease detection and essential in those with known A1ATD siblings. Other tests include a functional assay of alpha1 antiprotease which measures the ability of the patient's serum to inhibit human leukocyte elastase, chest imaging (CXR, HRCT chest). A hint to know, serum alpha one anti-trypsin (A1AT) concentration alone is not sufficient for the diagnosis yielding a low sensitivity. Also, liver biopsy is not necessary for the diagnosis and is even non-specific. [25, 26].

#### *What about treatment options/availability?*

There is no specific treatment for alpha one anti-trypsin deficiency (A1ATD)-associated liver disease. However, several treatment strategies targeting different pathways involved in the disease pathophysiology are under investigation; enzyme replacement and augmentation therapies are beneficial in those affected with lung disease and are also available. Recent ongoing technologies for the treatment of alpha one anti-trypsin deficiency (A1ATD) may show promising results such as autophagy, small molecule chaperones, gene repair therapy, RNA technologies, or cell transplantation. Furthermore, a recent study had been published in *The New England Journal of Medicine NEJM* evaluated the efficacy of Fazirsiran; An RNA interference gene therapy that inhibits alpha one anti-trypsin (A1AT) production in hepatocytes and concluded that it has not only reduced the defective alpha one anti-trypsin (A1AT) accumulation and liver damage but, in some cases, promoted liver fibrosis regression [26, 27].

## Conclusion

In summary, an important take-home message regarding the previously mentioned metabolic disorders should be clear in every physician's mind. First, Wilson's disease has been found globally, with a prevalence of around one in every 30,000 live births. The diagnosis should be

suspected in any case with unexplained liver, neurologic, or psychiatric abnormalities. Screening all siblings and children of Wilson's disease patients is a must. Treatment is lifelong with special considerations for special situation management.

HFE-related hereditary hemochromatosis H.H is the commonest cause of 1ry iron overload. The p. Cys282Tyr (p.C282Y) variant homozygosity is the most recognized in HFE-related hereditary hemochromatosis H.H mainly in the European population. Men are more frequently affected than women and disease prevalence increase with age. Genetic testing's indications should be addressed well.

Finally, alpha one anti-trypsin deficiency is not a rare disease. The clinical presentation relies on the type of mutation linked to alpha one anti-trypsin deficiency A1ATD. The diagnosis needs a high index of suspicion as it is often missed. There is no specific treatment for A1ATD-associated liver disease, but new therapies have shown promising results.

#### Abbreviations

| | |
|---|---|
| UCHID | United Conference of Hepatogastroenterology and Infectious Diseases |
| A1ATD | Alpha one anti-trypsin deficiency |
| WD | Wilson's disease |
| H.H | Hereditary hemochromatosis |
| NEJM | New England journal of medicine |
| COPD | Chronic obstructive pulmonary disease |
| FHF | Fulminant hepatic failure |

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#### Authors' contributions

T. Y., H. S., M. E., M. El-S., A. I., and N. B. collected, designed the research data, and wrote the manuscript with critical final revision and editing. The author(s) read and approved the final manuscript.

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#### Availability of data and materials

The data were generated and analyzed from several studies as mentioned in the references; if any data is needed, it will be available from the corresponding author upon reasonable request.

## Declarations

#### Ethics approval and consent to participate

Ethics approval was obtained from the UCHID ethical scientific committee for publication.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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## Publisher's Note