Aboalam *et al. Egyptian Liver Journal* (2022) 12:41
https://doi.org/10.1186/s43066-022-00205-z

Egyptian Liver Journal

REVIEW

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Wilson's disease clinic at the Assiut Liver Center in Egypt: a real well-established step on the way

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Abstract

Wilson's disease (WD) is a rare genetic disorder of copper metabolism that results in dysfunction of copper excretion into bile leading to its accumulation in the liver, brain, cornea, and kidney. Only a few epidemiological studies about WD have been carried out, with limited available data about the disease. The most common liver disease in Egypt is viral hepatitis, which masks other liver diseases, especially in adults. This review describes the establishment of the first specialized WD clinic in the Assiut Liver Center, Upper Egypt. This multidisciplinary clinic comprises stakeholders working in WD management from different specialties, including hepatologists, pediatric hepatologists, neuropsychiatrists, dieticians, radiologists, pathologists, and ophthalmologists. Over 2 years since the launch of the WD clinic in February 2020, a total of 64 WD suspected cases were referred to our center. The WD clinic at the Assiut Liver Center is a step to provide an integrated service for neglected diseases like WD. Besides the provided integrated services for WD patients, a family screening program is applied with satisfying results.

Introduction

Wilson's disease (WD) is a rare autosomal recessive genetic disorder of copper metabolism due to a mutation in the ATP7B gene on chromosome 13. This mutation results in the dysfunction of copper-transporting P-type ATPase responsible for copper excretion into the bile, leading to its accumulation in the liver, brain, cornea, and kidney [1].

Worldwide, very few population-based studies have examined the epidemiology of WD with an average prevalence of 1:10,000–30,000 with carriers of mutation about 1:90. However, it is more common (1 in 3000 to 10,000) in communities with a high rate of consanguineous marriage as in the Middle East (Druze, Iranian Jews, Palestinian) [2, 3]. Although the ability to diagnose and manage WD has improved globally, estimation of its actual prevalence remains a challenge, at least partly due to the wide range of phenotypes presenting to various medical specialties and the lack of a single diagnostic test [4].

The current global and regional situation of Wilson's disease

Only a few epidemiological studies about WD have been carried out. Most cases are diagnosed before 40 years old. However, WD has been reported at ages 2 to 80 [5]. Clinical presentation of WD is variable, including hepatic and neuropsychiatric disease. Generally, patients are diagnosed with WD after experiencing hepatic symptoms. When patients present without specific symptoms or the initial symptoms are neurologic or psychiatric, the diagnosis of WD can be delayed. However, neuropsychiatric symptoms are pretty common, occurring in about a third

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of WD patients [6]. Studies have reported neurologic and psychiatric manifestations in up to 40% and 10–25% of patients, respectively, when diagnosed with WD [7]. Thus, research into neuropsychiatric aspects of WD is currently receiving attention. WD is a treatable disorder, so early recognition and treatment are mandatory as delayed diagnosis may lead to fatal outcomes [8].

In the Arab world, few studies on WD from Lebanon, Egypt, Saudi Arabia, and Oman have been published. No mutation characteristic of the region was identified. Most patients from Egypt and Saudi Arabia consistently show a high prevalence of consanguinity and homozygosity. Lebanese and Egyptian patients share missense mutations in exons 8, 10, 18, and 19 [9–12]. The predominant phenotype of WD in the region was also hepatic, suggesting the benefits of screening for WD in patients with unexplained hepatic dysfunction.

Egypt's most common hepatic disease is viral hepatitis (hepatitis C), with the highest prevalence worldwide [11]. Accordingly, it masks other liver diseases, especially in adults; therefore, the current situation of WD is still challenging to state due to the scarcity of epidemiological data. WD might be falsely considered a rare, neglected disease probably due to a lack of physicians' awareness of its comprehensive range of clinical presentations and unavailability of diagnostic tools and therapy. Unfortunately, all these factors negatively affect the accessibility to WD patients and hence the proper management. Establishing a molecular diagnostic system with a precise algorithm and availability of that work in our area facilitates the management of those patients. It also helps the follow-up of the patients and reduces the time between shipping the samples and receiving the results.

Wilson's disease clinic in the Assiut Liver Center

The last official records in 2020 show Upper Egypt has almost 20 million inhabitants [13]. The Assiut University is considered one of the largest and oldest universities in Egypt, which provides healthcare services to a large population sector in Upper Egypt. The Assiut Liver Center, affiliated with the Egyptian Ministry of Health, is considered one of the important referral centers for all liver diseases. This center offers different services for its patients through 5 outpatient clinics: viral hepatitis clinic, hepatocellular carcinoma clinic for screening and treatment, nonalcoholic fatty liver disease (NAFLD), and nutrition clinic. In addition, there is a sizeable radiological unit equipped with three advanced ultrasound machines, a FibroScan machine (for fibrosis assessment), and an in-body device (for nutritional assessment through body composition analysis). The center also has a well-equipped laboratory and pharmacy managed by clinical pathologists and pharmacists. Ten years ago, a medical data management unit was established to have an excellent archiving system for our patients and hence help in statistical analysis and clinical research. Unfortunately, there is neither an inpatient ward nor intensive care unit, but the gastrointestinal endoscopy unit is under reconstruction.

Unfortunately, WD patients in Upper Egypt struggle to find a specialized center due to the problematic accessibility as there are no specialized centers for genetic diseases in their area. Hence, they must travel a long distance (300–800 km) seeking medical consultations and proper management in Cairo.

In February 2020, a specialized WD clinic was established in the Assiut Liver Center. This clinic appropriately manages such a rare disease with different clinical presentations. The outpatient clinic receives patients weekly, followed by a weekly meeting for the multidisciplinary team (MDT). This MDT includes hepatologists [4 consultants (MD) & 5 specialists (M.Sc.)], a pediatric hepatologist, a neuropsychiatrist, a dietician, a radiologist, a pathologist, and an ophthalmology consultant. This highly specialized MDT is responsible for discussing and making final decisions for all cases. Also, our specialized WD clinic cooperated with the Pathology Department at the Assiut University, the Ophthalmology Department at the Al-Azhar University, the Pediatric Hepatology Unit at the Assiut University Pediatric Hospital, and Hepatology and Liver Transplantation Units at the Al-Rajhi University Hospital. Patients who required admission were to be referred to these hospitals.

WD clinic receives most of its patients as a referral from primary, secondary, or even tertiary healthcare units and related specialties of the private sector. Confirmed WD patients will start the treatment and their regular follow-up visits at the outpatient clinic immediately, and whenever hospital admission is required, they will be hospitalized at the Assiut University's hospital (Fig. 1). All required patient management steps are performed in our center, including history taking, thorough clinical examination, required laboratory investigations, related imaging studies, liver biopsy if indicated, and histopathological examination. Upon completing the patient's medical record, the case will be scheduled for discussion in the next MDT meeting.

Our MDT depends on the European Association for Study of the Liver (EASL 2012) and American Association for the Study of Liver (AALSD 2008) guidelines for diagnosing and managing WD cases. Leipzig score [14] (adapted from the scoring system developed at the 8th International Meeting on Wilson's Disease 2001) had been advocated by both EASL and European Society for Pediatric, Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines to establish a diagnosis of

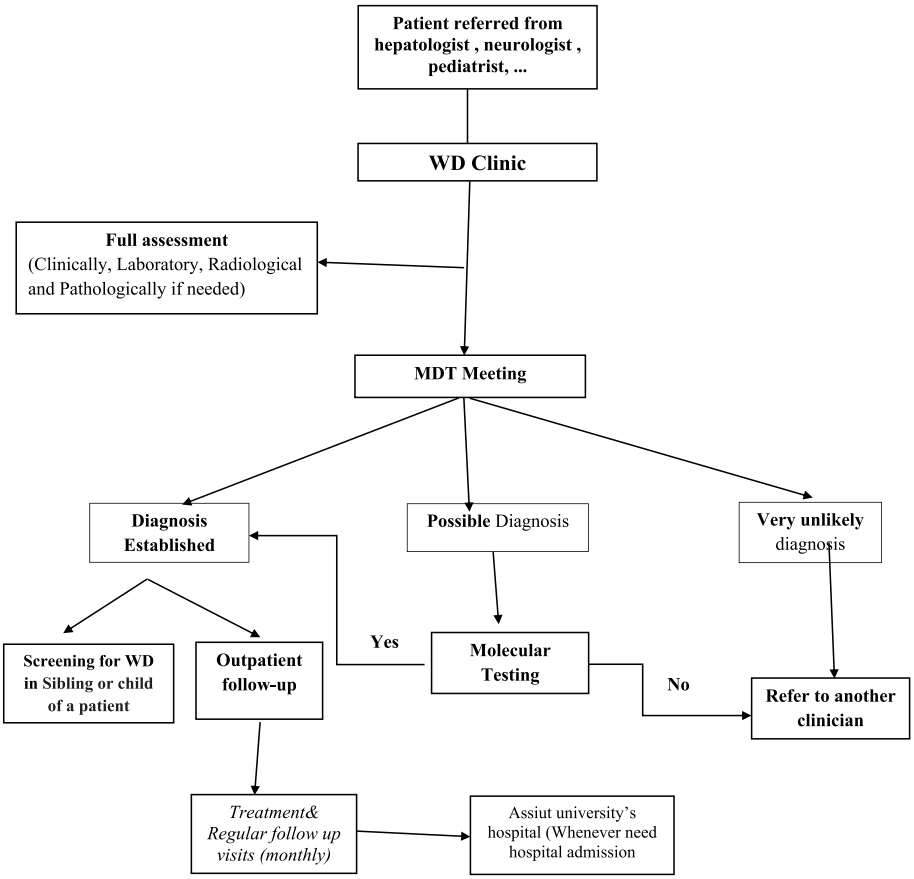

Fig. 1 Flowchart for the WD patient's pathway in the Assiut Liver Center

WD, and it was also validated in adult and pediatric populations [15, 16]. Leipzig's scoring system includes a combination of clinical, biochemical, and genetic testing [14]. Interestingly, EASL guidelines propose a slight variation on the interpretation of this score, whereby scores of 2 are classified as unlikely rather than probable as in the original scoring system. To definitively rule out the diagnosis of WD, they recommend that unlikely and possible cases be stratified based on urinary copper excretion, hepatic copper content, and *ATP7B* mutational analysis [17].

One of the main targets of our center is the application of a family screening program for patients with WD. The first-degree relatives of WD should be genetically screened. First-degree relatives should include the previous generation, siblings, and the next generation. Genetic testing should be the primary screening method for family members if available. Although the relatives of a proband are more likely to be patients with WD, the diagnosis should be based on sufficient evidence to avoid unnecessary lifelong treatment.

Unfortunately, genetic testing is not routinely performed in our center, and hence, our screening program directed to patients' families depends mainly on thorough clinical examination, serum transaminases, serum ceruloplasmin, 24-h urinary copper, and liver ultrasound as an initial step. If there is any suspicion for WD, the second step includes slit lamp ophthalmological examination, MRI brain, penicillamine challenging test, and liver biopsy for histological assessment as a final step if indicated. About one-fifth of the cases were diagnosed with satisfying results through this family screening approach.

In our center, well-established administrative and logistic procedures provided a low-priced investigation (ceruloplasmin, 24-h urinary copper) and treatment (D penicillamine and zinc) package for the patients. In addition to the official announcement of our new specialized WD clinic for all the health caregivers, specially hepatologists, specialized neuropsychiatric clinics, and pediatric hospitals in Upper Egypt, using different tools such as scientific conferences, seminars, specialized WhatsApp

groups, and different awareness campaigns about WD for the physicians and patients was established.

Up to date, 64 cases have been referred, 42 were confirmed, ten were suspected WD, and 12 had different diagnoses. Among 42 confirmed WD cases, 27 patients are males aged 6–35 years old. The main manifestations of WD were hepatic in 26/42 patients, 11/42 patients had neuropsychiatric manifestations, and five patients had a mixed presentation.

Although the WD clinic at the Assiut Liver Center depends on the AASLD 2008 and Leipzig criteria (EASL 2012 and ESPGHAN 2018) for diagnosing WD, it is still challenging due to the high cost and unavailability of genetic study and quantitative copper in dry liver tissues [17–19].

Multiple diagnostic, therapeutic, and monitoring tools exist for patients suffering from WD. While many patients are diagnosed and adequately assessed with currently available methods, others are still in a diagnostic uncertainty characterized by borderline ceruloplasmin levels, inconclusive genetic findings, and unclear clinical phenotypes. Patient prognosis is based on early diagnosis and adequate long-life therapy. Therefore, delay in diagnosis and starting decoppering treatment can result in disastrous consequences.

Conclusion

Our aim in WD specialized clinic at the Assiut Liver Center is to initiate efforts aiming to closely evaluate the current situation of WD in Egypt, primarily upper Egypt, based on our database, including the epidemiological data as incidence and prevalence rates, in addition to data related to the efficacy of the diagnosis and treatment protocols. Changes in the diagnostic criteria, including gene analysis and quantitative serologic study, enabled by the progression of diagnostic technology, have created a need for new epidemiological studies of WD. From our point of view, a nationwide registry for metabolic and genetic liver diseases, including WD, is highly required in our country. We consider the WD clinic at the Assiut Liver Center as one of the early steps to achieving this goal, and we are striving to share this work through collaboration with other relevant specialized hospitals and research centers in Egypt.

Abbreviations

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for Study of the Liver; ESPGHAN: European Society for pediatric, Gastroenterology, Hepatology and Nutrition; MDT: Multidisciplinary team; NAFLD: Nonalcoholic fatty liver disease; WD: Wilson's disease.

Acknowledgements

None

Authors' contributions

HSA, ME, and MEK conceptualized the idea. MKH, NFI, WH, AMA, AE, EGAA, and HFH were responsible for patient follow-up and data acquisition. HAS, ME, MEK, and NE wrote the first draft of the manuscript. The authors read and approved the final manuscript.

Funding

This is a non-funded work.

Availability of data and materials

No data set was generated for this work.

Declarations

Ethics approval and consent to participate

Non-applicable, being a review article with no patient-related data

Consent for publication

All authors agree to the journal rules for publications.

Competing interests

The authors declare that they have no competing interests.

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Received: 16 February 2022 Accepted: 17 July 2022
Published online: 20 July 2022

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