WILSON DISEASE: CLINICAL CHARACTERISTICS, DIAGNOSIS, AND MANAGEMENT

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Abstract

Wilson disease is a rare genetic disease, affecting multiple systems. The cause of the disease are mutations in ATP7B gene and is inherited in an autosomal recessive manner according to Mendel's laws. Mutations in ATP7B gene cause a decrease in copper secretion and consequently copper hyperdeposition in many tissues and organs. The main clinical manifestations come from the liver and the central nervous system, but a plethora of other organs may be involved. The diagnosis can be established using the Leipzig criteria, but the final diagnosis requires genetic testing. Chelation therapy is the main treatment, but secondary manifestations require specific management. Although to date there is no effective treatment, the symptoms of the disease can be treated adequately with the existing treatments and patients usually have a good quality of life.

Introduction

Wilson disease (WD) or hepatolenticular degeneration is a rare hereditary disease which affects mainly liver and central nervous system (CNS) [1] while it rarely also affects other organs or systems [2]. The disease has a clear genetic background and it is inherited following the autosomal recessive manner according to Mendel's laws [1]. The disease prevalence is approximately 30 cases per million and the presentation age has a spectrum between 3 and 60 years. It was first described by Wilson in 1912 as a progressive lesion of the lenticular nucleus and liver with the main clinical manifestation being an early-onset dystonia. Earlier, Westphal described the pseudosclerotic form of the disease and in time it was perceived that parkinsonism is a key clinical symptom of the disease [1].

Genetic

Wilson disease is a genetic disease. From its first description, this disease was considered as a familial disease. The Wilson's disease gene was mapped to chromosome 13q14.3 and the causative gene was identified as ATP7B in 1985, and contains 21 exons [3, 4]. The ATP7B gene encodes a copper transporting (6 Cu molecules), P-type transmembrane ATPase that is highly expressed in the liver and kidney. Several missense mutations, small deletion/insertion in the coding region or splice junction mutations are responsible for the clinical expression of the WD. Although mutations have been described in almost all exons, the exons 8 and 14 are the mainly affected [5] (most common mutations are the R778L and the H1069Q) [6]. Studies suggest that 90-98% of patients with WD are heterozygotes with compound heterozygous mutations [6].

Pathophysiology

The protein which is encoded by ATP7B gene plays a key role in the pathophysiology of the disease. The ATP7B protein is a copper transporting, P-type transmembrane ATPase. The normal function of ATP7B protein seems to be the incorporation of copper into cell organelles leading to the production of ceruloplasmin and secretion of copper into the bloodstream, where excessive copper is excreted to the bile [7]. As a result of mutations in the ATP7B gene, the liver is not capable of excreting copper into bile and a positive copper balance is established. That leads to the accumulation of copper firstly in the liver and then in other parts of the body, such as in the brain [7, 8].

Clinical presentation

Hepatic Features

Wilson disease mainly affects the liver. The accumulation of copper in the liver leads to degeneration and failure of the organ. Manifestations of liver disease can be divided into some distinct categories of degeneration which present significant differences among them.

Liver disease can be completely asymptomatic and is usually identified due to hepatomegaly or during the screening process because patients have discretely elevated transaminase levels in serum [9]. Some patients present with simple, acute, self-limited hepatitis-like disease with anorexia, fatigue, and abdominal pain [10]. Rarely, WD can occur as autoimmune hepatitis, with arthropathy, malaise, fatigue, and rashes. This manifestation of WD responds well to chelation therapy even if cirrhosis is present [9, 10]. Other patients present with mild to moderate degree fatty liver disease presenting abnormal liver function [10]. Moreover, serum unbound copper, in high concentrations, may cause either acute or chronic hemolysis, leading to the manifestation of hemolytic anemia. Liver disease, as well as Kayser-Fleischer rings, are likely to be present. Recurrent hemolysis further predisposes to cholelithiasis, even in children, and recurrent episodes of jaundice [9-11]. Acute hepatitis in WD is rare and when it occurs, it presents with jaundice, elevated transaminase levels, and hepatic failure with coagulopathy. Direct Coombs test-negative hemolytic anemia may coexist with acute hepatitis. Hemolysis is thought to occur secondarily to marked copper release into the bloodstream due to the acute hepatic necrosis [7, 9]. The disease typically manifests as chronic active hepatitis which slowly progresses and leads to cirrhosis and portal hypertension [9, 10].

Neurological presentation

The disease affects various structures of the CNS. It mainly affects the basal ganglia but also the cerebellum and structures of the pons. In about 20% of WD patients, the disease presents with neurological symptoms [12].

Parkinsonism

Extrapyramidal manifestations of the disease, described in 62% of patients with WD, include dysarthria, resting tremor and gait disorders [1]. Extrapyramidal symptoms in WD resemble those of idiopathic Parkinsonism with typical half-body asymmetry [1, 12].

Dystonia

Dystonia is consider as a common symptom in patients with WD (65%) [13] and its onset should raise the suspicion of the disease. It could be focal, multifocal, and even generalized, while it can evolve from focal to generalized during the course of the disease [1, 12]. Sardonic laugh is a typical clinical presentation of dystonia affecting the muscles of the head. When the laryngeal muscles are affected, it may lead to speech disorders and the characteristic dystonic dysarthria [12].

Tremor

Tremor is a prominent manifestation of the onset of WD [7]. Wilsonian tremor can occur at rest, upon assumption of posture or with action. The arms are most frequently involved but the head and the legs can also be affected. In Wilsonian tremor, asymmetry prevails. The kinetic tremor is a medium to high frequency tremor. The classical posture-induced wing-beating tremor is a lower frequency tremor concerning the upper limbs [1, 2, 12].

Dysarthria

Dysarthria is probably the most common neurologic manifestation of WD. In patients with dysarthria, dysphagia frequently coexists and usually stems from dystonic vocal cords, dystonia of other head muscles, or tremor. Ataxic dysarthria is a less common manifestation of the disease [1, 2, 10, 12].

Choreoathetosis

Chorea is a common finding in early-onset WD. Choreic movements are irregular involuntary movements that appear at rest and they are superimposed on or interrupt normal movements. Chorea symptoms range from minor movements to severe uncontrolled movements affecting muscles of the head and the arm [1, 12].

Ataxia

Ataxia has been reported in 30% of patients with WD and it presents as hypermetria of the limbs and extraocular muscles [1, 10, 12].

Other neurologic features

Moreover, in WD cognitive decline, myoclonus, and tics have also been reported [1, 10, 12].

Psychiatric features

When psychiatric manifestations are the only symptom of WD, they are usually attributed to other causes and rarely raise the suspicion of the disease. Diagnosis of WD during this period is rare. At the onset of the disease, the most common psychiatric symptoms have been reported to be personality change, incongruous behavior, irritability, and delusional thoughts [1, 10]. At the same time cognitive impairment may occur with memory impairments and executive dysfunction [1]. Many patients present with self-harm ideas especially after the diagnosis is confirmed [10].

Ophthalmologic manifestations

Copper deposits in the paralimbal area of the cor-

Table 1. Neurological manifestations of WD

Neurological symptoms	***Characteristics***	***Percentage (%)***
Parkinsonism	Dysarthria, resting tremor, gait disorders, usually symmetrical	62 %
Dystonia	Focal, multifocal, generalized, dystonic dysarthria	65 %
Tremor	Resting tremor, kinetic tremor medium to high frequency, posture tremor lower frequency	30%
Dysarthria	In patients with dystonia, salivation coexists, ataxic dysarthria (uncommon)	30%
Choreoathetosis	Young onset, range from large to fine choreic movements, commonly affects head and arm muscles	10%
Ataxia	Dysmetria in upper limbs and eyes (nystagmus)	30%
Other	Cognitive decline, myoclonus, and tics	98%

nea, known as Kayser- Fleischer (KF) rings, which are seen in almost all patients with neurologic WD. KF rings are observed in the border region where the cornea transitions to the sclera and upon treatment, the intensity of the copper deposits is reduced [1, 2]. Occasionally, sunflower cataract may be observed upon slit lamp examination.

Other manifestations

As the disease is multisystemic, several other organs and tissues may be affected. Low-molecular weight proteinuria with microscopic hematuria, and Fanconi syndrome are common kidney manifestations. Furthermore, copper accumulation in synovial membranes can cause arthritis of large joints [10, 14]. In approximately 10% of affected individuals, reduced bone mineral density with a prevalence of osteoporosis is observed [10]. Less common manifestations of WD are rhabdomyolysis of skeletal muscles, cardiac arrhythmias, pancreatitis, cardiomyopathy, and various endocrine disorders [9, 10].

Depending on the manifestations and the age of onset, various classifications of the disease have been proposed. The main classification used concerns the onset symptomatology, as it shown in Table 2 [11].

Diagnostic workup

Early-onset extrapyramidal involvement should always raise suspicion of WD. The most common screening method is the evaluation of serum ceruloplasmin levels. Ceruloplasmin is usually low, although in approximately 10% of patients it may be marginally normal or even normal [2]. However, in children lower levels of ceruloplasmin have been detected in comparison to adults [10]. Of great importance is also the evaluation of copper levels in a 24-hour urine test. In symptomatic patients copper levels in urine are always increased to a value greater than 100 mcg/day while the normal levels are below 50mcg/day [9]. Given the increased incidence, every patient should be examined for KF rings during the work-up [10]. Most patients have decreased levels of serum copper, that reflects the decreased levels of serum ceruloplasmin. Thus, the measurement of non-ceruloplasmin-bound copper is essential [15, 16]. The excess in serum non-ceruloplasmin-bound copper is indicated by the combination of low ceruloplasmin serum concentration and a normal or high serum copper concentration [10]. Although not always reliable for diagnosis, due to its high dependency on the accuracy of both the serum ceruloplasmin concentration and the serum copper concentration, high serum non-ceruloplasmin-bound copper concentrations often reflects copper overload [9, 10]. In case of hepatic impairment, indicated by abnormal liver biochemistry tests, liver biopsy is recommended. In addition to liver damage, a biopsy may also detect and quantify copper deposition [8, 9].

If the laboratory tests strongly supports WD, a genetic test should be performed to confirm the diagnosis [2, 5, 9, 10]. Genetic testing may include single gene testing, a multigene panel, and more comprehensive genomic testing [1, 10].

Magnetic resonance imaging (MRI) of the brain is characterized by high intensity T2 signal lesions on basal ganglia and white matter, as well as high intensity T1 signal lesions caused by hepatic encephalopathy [1, 12].

Finally, dopamine transporter (DaT) scan has an auxiliary role in the diagnosis of WD by revealing the decreased uptake of radiotracer in the striatum [1].

Laboratory findings alone are not sufficient for establishing the diagnosis. Therefore, the Leipzig criteria, which combine clinical, laboratory and imaging parameters, are used. According to the Leipzig criteria, more than 4 points are required in order for the WD diagnosis to be established, while an alternative diagnosis should be considered in patients with less than 4 points. Based to the criteria, genetic testing

Table 2. Classification of WD

Clinical presentation	Onset Symptomatology
No neurologic presentation	
Preclinical	Non, preclinical diagnose
Hepatic	Acute or chronic hepatic lesions / cirrhosis
Pseudo-parkinsonism (stiffness, tremor)	Slow motion, stiffness, diminution, position / energy / rest / orthostatic tremor, postural reflex disorder, dysarthria, salivation
Pseudo-sclerotic (tremor)	Position / energy / calm / orthostatic tremor, ataxia, dysarthria
Mix (chorea-athetosis non rhythmic)	Chorea, athetosis, dystonia, parkinsonism
Psychiatric	

Table 3. Leipzig criteria

Signs/Symptoms	Score
Kayser-Fleischer ring	
present	2
Absent	0
Neurological symptomatology or finding in MRI	
Severe	2
Mild	1
Absent	0
Ceruloplasmin	
Normal range (.0,2g/L)	0
0.1-0.2 g/L	1
< 0,1g/L	2
Coombs negative hemolytic anemia	
Present	1
Absent	0
Liver Copper	
> 4μmol/g2	2
0.8-4μmol/g1	1
< 0.8μmol/g	-1
Rhodamine positive granules	1
Rhodamine positive granules	1
Urine Copper excretion	
Normal	0
1-2 times ULN	1
> 2 times ULN	2
5 times ULN after penicillamine	2
Mutation analysis detected	
Both chromosomes	4
One chromosome	1
No mutations	0

Score	Classification
≥ 4	Disease
3	Possibility of disease
≥ 2	Absence of disease

and liver biopsy may not be necessary if other test results add up to 4 points at least [9].

Differential diagnosis

The differential diagnosis of WD includes a great variety of diseases with hepatic and neurological manifestations similar to those of the disease.

Concerning hepatic manifestations, the differential diagnosis includes:

- Chronic viral hepatitis.
- Primary sclerosing cholangitis.
- Non-alcoholic steatohepatitis (NASH).
  Note: patients thought to have NASH, should have WD excluded due to available treatment.
- Autoimmune hepatitis.
- *HFE*-associated hereditary hemochromatosis.
- Drug hepatotoxicity.
- Alcoholic liver disease.
- Alpha-1-antitrypsin deficiency.
- Primary biliary cirrhosis.

Concerning neurologic manifestations, the differential diagnosis includes:

- Essential tremor.
- Parkinson disease.
- Dentatorubro-pallidoluysian atrophy.
- Huntington disease.
- Hyperthyroidism.
- Dopa-responsive dystonia.
- Neurodegenerative diseases.
- Inherited forms of dystonia.
- Hereditary ataxias.
- Drug effects or toxicity.
- Niemann-Pick disease type C [2, 10].

Treatment

The purpose of the treatment in WD is on one hand the reduction of the excess of serum copper and on the other hand the symptomatic treatment.

Early initiation of treatment in asymptomatic patients could prevent the onset of several disease manifestations. The removal of excess copper is achieved with chelating agents. D-penicillamine is used as the drug of choice. It binds circulating copper, reduces the affinity of copper for proteins and releases it from tissues. It also promotes the synthesis of metallothionein that binds copper and is excreted in the urine [9]. Improvement in liver function was shown in 90% of patients with hepatic impairment, while only 55% of patients with CNS involvement were improved [1, 9, 10]. Furthermore, treatment with D penicillamine, was found to worsen pre-existing symptoms, in 10-50% of the patients, which led to the recommendation of a gradual dose increase with a starting dose of 125 mg/day [1]. The maximum daily dose is 750mg-1000mg/day.

An alternative treatment is trientine which acts like D-penicillamine. Usually, the daily dose is 900-2700mg, but recent studies suggest a bolus daily dose 15mg/KBW. Trientine is better tolerated but has been associated with worsening of the initial neurological symptoms in higher rates than D-penicillamine [1, 9, 10]. Both drugs should be administered separately from other drugs and food in order to avoid absorption disorders of the drugs [9, 10]. Zinc supplements also play an important role in the treatment of the disease. Zinc promotes the synthesis of metallothionein in the intestine and increases the excretion of copper. The daily dosage is 50mg three times a day. Co- administration with chelating agents should be avoided because its action is neutralized [1, 7, 9, 10]. Finally, tetrathiomolybdate ammonium is another therapeutic option in neurological manifestations of WD. Tetrathiomolybdate reduces copper levels by reducing its absorption from the intestine, but also promotes its binding to bile-secreting proteins [10, 17]. During treatment, monitoring of the excretion of copper in 24-h urine samples is important. Urine copper should be evaluated every 2 weeks during the first 6 weeks of treatment, and every three months in the next 12-month period [9].Consumption of foods rich in copper, such as liver, brain, chocolate, mushrooms, shellfish, and nuts should be avoided [10].

Concerning the symptomatic treatment of neurological manifestations, administration of levodopa for the treatment of extrapyramidal symptoms as well as anticholinergics for the treatment of dystonia is of great importance. Moreover, psychiatric assessment is considered necessary when psychiatric manifestations are present [1].

Follow up

Lifelong follow up of the patients with WD is important. Usually, evaluation of serum copper levels and ceruloplasmin levels at least twice per year is required for further evaluation. Moreover, liver biochemistry testing, international normalized ratio (INR), urinalysis, complete blood count, and physical examination including neurologic assessment are also of an essential need. In patients with WD under chelation therapy, monitoring with urinalysis and complete blood count are required more often. An annual evaluation of urine copper levels in 24-hour urine test samples is also required. More frequent evaluation of the above is recommended in cases of poor compliance or in dosage adjustment [1, 9, 10, 17].

Conclusion

Wilson disease is a rare and severe multisystem genetic disease with no etiologic treatment. Furthermore, the established treatment options have several limitations. However, both early diagnosis and rapid initiation of treatment are of paramount importance to avoid irreversible organ and tissue lesions as well as to avoid the accumulation of disability. Further studies promise better and effective treatment options.

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