Review Article

Epidemiology, Evaluation and Management of Wilson Disease; Review Article

Abstract:

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive ailment characterized by aberrant copper buildup in the body, with the brain, liver, and cornea being notably affected.Wilson was the first to discover WD in 1912. The first two instances of WD in China were reported by Cheng. After the 1950s, WD research exploded, and the number of documented cases progressively caught up to those of Western nations.Wilson illness is caused by a mutation in the ATP7B gene on chromosome 13, which regulates the protein transporter that excretes excess copper into the bile and out of the body. So far, over 500 mutations have been discovered. The most common treatment for WD is D-penicillamine (D-PCA). Patients with severe spasms, deformities, or dysphonia, as well as those who are allergic to D-PCA, should avoid it.Family screening is recommended because early detection is critical for initiating therapy in the early, asymptomatic stages of the disease, rather than when liver decompensation or extensive neurological irreversible harm has already occurred. In this circumstance, the optimum technique is to finish copper investigations in the index patient's first- and second-degree relatives. In this article we we'll be discussing disease prevalence, diagnosis and management.

Introduction:

Wilson disease (hepatolenticular degeneration) is a rare autosomal recessive ailment characterised by aberrant copper buildup in the body, with the brain, liver, and cornea being notably affected. It affects one out of every 30,000 people and can cause weakness, stomach discomfort, jaundice, personality changes, seizures, and other symptoms. [1]

The brain and liver are generally involved in the symptoms. Vomiting, weakness, ascites, swelling of the legs, yellowish skin, and itching are all indications of a swollen liver. Tremors, muscular stiffness, difficulty speaking, personality changes, anxiety, and auditory or visual hallucinations are examples of brain or neurological symptoms. Wilson disease is caused by a mutation in the Wilson disease protein (ATP7B) gene, which is autosomal recessive. A copy of the gene from each parent must be inherited for a person to be impacted. Blood tests, urine tests, and a liver biopsy, as well as a clinical examination, are used to make the diagnosis.Family members of people who are sick may be screened through genetic testing. [1]

Wilson was the first to discover WD in 1912. The first two instances of WD in China were reported by Cheng. After the 1950s, WD research exploded, and the number of documented cases progressively caught up to those of Western nations.On chromosome 13q14-21, the gene that causes WD is found. This gene, ATP7B, codes for a P-type ATPase involved in ceruloplasmin production and copper excretion. Pathogenic mutations in ATP7B impair the normal structure or function of enzymes, causing copper accumulation in various organs and resulting in a variety of clinical symptoms. Misdiagnosis is widespread due to the disease's many symptoms.Many scientists have tried to figure out how the genotype and phenotype of WD are related. Dong et al. discovered 58 novel mutations and created the first Chinese ATP7B pathogenic mutation spectrum between 2004 and 2015. [2,3-8]

The genetic abnormality is found on chromosome 13's long arm (13q), which has been proven to affect the copper transporting ATP gene in the liver. The majority of Wilson disease patients develop liver impairment in their first ten years of life. In the third/fourth decade of life, neuropsychiatric symptoms appear. Wilson illness is uncommon, yet it is lethal if not diagnosed and treated. [1]

The most common treatment for WD is D-penicillamine (D-PCA). Patients with severe spasms, deformities, or dysphonia, as well as those who are allergic to D-PCA, should avoid it. In China, dimercaptosuccinic acid (DMSA) was the first medicine used to treat WD. For individuals with significant neurological symptoms, DMSA is indicated as an alternative. Monozygous treatment is also appropriate for asymptomatic WD, as well as maintenance therapy when copper chelating drugs have been used.Because WD is a hereditary illness that may be treated, the majority of individuals have a good prognosis. Although the frequency of WD in China is higher than in Western nations, clinical studies are scarce in China, and therapy is frequently relied on expert opinion and data from other countries. As a result, specialised therapies for Chinese patients with WD must be researched and provided. [2,9-11]

Etiology:

Wilson illness is caused by a mutation in the ATP7B gene on chromosome 13, which regulates the protein transporter that excretes excess copper into the bile and out of the body. The protein transporter is found in the liver and brain's trans-Golgi network. Copper is excreted mostly (95 percent) through the liver. Excess copper builds up in the liver, then leaks into the bloodstream, eventually affecting other organ systems. Excess copper induces the production of free radicals, which cause the oxidation of essential proteins and lipids. The mitochondria, nuclei, and peroxisomes are the first to alter. [1]

Epidemiology:

With a gene frequency of 0.56 percent, the prevalence of WD, a rare illness, is comparable in most world locations, equal to around 0.5 cases per 100000 population, or the most frequent number 30 cases per million. Nonetheless, the condition is far less prevalent in other areas/countries, with specific mutations being reported more commonly in some groups. So far, over 500 mutations have been discovered, and the lower number of clinically evident instances compared to the frequency of allele carriers in the population likely reflects the mutations' lesser penetrance. [12-16]

This illness affects 1 in every 30,000 people, with 1 in every 90 people being a carrier. Wilson illness is more common in some groups due to a higher percentage of consanguinous marriages. Males and females are both impacted in the same

way. The typical age of onset is four to forty years old, however this illness has been found in infants as young as three and individuals as old as seventy. [1]

In 1968, Sternlieb and Scheinberg estimated the prevalence of WD to be 5/1,000,000. Bachman et al. researched WD in Leipzig, Germany, from 1949 to 1977, and found that the frequency of WD was 29/1,000,000 births. According to Saito, the frequency of WD was 33/1,000,000 newborns in 1981. In 1991, Park et al. used computerised hospital data, survey findings, and death certificates to try to figure out how common WD was in Scotland. In a population of 5,090,700 people, they found 21 cases with WD, resulting in a prevalence of 4/1,000,000.Reilly et al. utilised a similar methodology to evaluate the prevalence of WD in the Republic of Ireland in 1993, and they found 26 cases during a 19-year period.In five of the cases, patients died before receiving a definitive diagnosis. The adjusted birth rate of people with WD was 17/1,000,000 between 1950 and 1969, corresponding to a gene frequency of 0.41 percent and an incidence of heterozygotes of 0.82 percent. To obtain a minimal illness estimate, the gene frequency was updated to 0.36 percent and the incidence of heterozygotes was modified to 0.72 percent to account for the greatest degree of kinship. [2,17-22]

So far, over 500 mutations have been discovered, and the lower number of clinically evident instances compared to the frequency of allele carriers in the population likely reflects the mutations' lesser penetrance. In Europe and North America, the most prevalent mutations are His1069Glu (H1069Q), Arg778Leu in South Korea, Japan, and China, 2007del7 in Iceland, and Met645Arg in Spain. The illness is most common in Germany (2.5/100000 people), Japan (3.3/100000 people), and Austria (3.0/100000 people). Costa Rica, on the other hand, has the highest incidence rate in the world (4.9/100000 people).The most common mutation is Asn 1270 Ser, which was previously exclusively seen in Sicilian, Lebanese, and Turkish populations, probably due to increased consanguinity and a potential founder effect. The second place with a high prevalence (estimated 1/10000-1/7000) is Sardinia, where a well-documented founder mutation (-441/-427del) is widely frequent (67%) and all other mutations have a relative frequency below 10%. [2,23-36]

Evaluation:

Molecular diagnostics (laboratory diagnosis), diagnostic imaging, and genetic analysis are all used to diagnose WD. The use of molecular diagnostics has risen. Liver illness, brain and nerve system damage, osteoporosis, and K-F rings are all clinical symptoms of WD. It's possible that liver damage will go undetected. Routine liver function tests do not provide diagnostic information. Tremors can help doctors diagnose WD that affects the neurological system. Patients with neurological or mental symptoms are more likely to be diagnosed with WD. The existence of K-F rings near the cornea's edge can also be used to diagnose the condition. [2]

a ceruloplasmin level test can be ordered if you a strong suspicion of Wilson illness is present . It will be below 20 mg/dL (normal range is 20 to 40 mg/dL). Copper levels in the urine will be increased by more than 100 mcg/dL. These two lab results with Kayser-Fleischer rings are generally adequate to diagnose Wilson disease, but if another diagnosis is possible, schedule a liver biopsy to check for liver copper levels; this is the most accurate test for Wilson disease. Any protein deficient condition can cause low amounts of ceruloplasmin. A copper level more than 250 mcg/g of dry liver tissue indicates a good outcome. The use of an MRI to screen for brain involvement is beneficial. Elevated AST and ALT levels cause liver function tests to be abnormal. [1]

The basal ganglia were the most commonly damaged regions on nuclear magnetic resonance imaging (MRI) of the brains of patients with WD. The caudate nucleus, thalamus, midbrain, pons, and cerebellum show hypointensity on T1-weighted imaging and hyperintensity on T2-weighted scans, but hyperintensity on T1-weighted images and hypointensity on T2-weighted images can occur in select rare situations. The basal ganglia, thalamus, and brainstem are more likely to experience simultaneous signal alterations.Patients with WD exhibit different degrees of frontal brain atrophy, ventricular enlargement, and hydrocephalus. Because the brain abnormalities observed on MRI might disappear after successful therapy, MRI is a helpful tool for monitoring treatment efficacy. [2]

Wilson illness should be considered if symptoms suggestive of the condition are present, or if a family member has been diagnosed with it. Most exhibited slightly elevated aspartate transaminase, alanine transaminase, and bilirubin levels, as well as mildly abnormal liver function tests. Because injured liver cells are unable

to make albumin, the prothrombin time is extended; similarly, the prothrombin time is prolonged because the liver is unable to create proteins known as clotting factors.Wilson-related acute liver failure patients had decreased alkaline phosphatase levels. If there are neurological symptoms, a T2 sequence MRI of the brain may reveal hyperintensities in the basal ganglia. The unique "face of the gigantic panda" pattern may be visible on MRI. [1]

Genetic testing has also become commonplace. Mutations in the ATP7B gene are the cause of WD. Direct sequencing analysis is currently the most accurate method of detecting ATP7B mutations. Point mutations are the most prevalent changes, although other types of mutations, such as minor deletions or insertions, entire deletions, and splice site alterations, have also been discovered. Previous research has suggested that WD in China is caused by a combination of common and unusual mutations. [2]

Family screening is recommended because early detection is critical for initiating therapy in the early, asymptomatic stages of the disease, rather than when liver decompensation or extensive neurological irreversible harm has already occurred. In this circumstance, the optimum technique is to finish copper investigations in the index patient's first- and second-degree relatives.

Treatment:

Treatment should preferably begin soon after diagnosis in pre-symptomatic patients (where testing is done as part of a screening for afflicted family members) or immediately following rapid diagnosis in symptomatic people. If therapy is started early enough, deterioration can be avoided, and life expectancy can be equivalent to that of those who do not have the condition. Patients with WD have a good prognosis if they stick to their treatment regimen. On the contrary, the disease's natural course is nearly often marked by gradual, unrelenting deterioration, eventually leading to death from liver or brain disease.Discontinuing medication can be fatal, putting the patient at risk of FW and increasing mortality, as shown in a research in which 8 of 11 patients who stopped receiving treatment died on average 2.6 years later. [12]

D-penicillamine (chelator): D-penicillamine has been used as a first-line therapy for Wilson disease since the 1950s. It is taken as tablets two or three times a day. Pyridoxine and D-penicillamine must be administered together. To confirm

chelation and enhanced copper excretion, 24-hour urine copper excretion is employed. Urinary copper levels should be five to 10 times normal; if they're lower, noncompliance may be a problem, or body copper reserves may have been depleted sufficiently. [37]

- During D-penicillamine treatment, a complete blood count and urinalysis must be checked on a regular basis. Serious adverse effects, such as severe thrombocytopenia, leukopenia, aplastic anaemia, proteinuria, nephrotic syndrome, polyserositis, Goodpasture syndrome, and severe skin reactions, can occur in up to 30% of people. It's possible that an allergic reaction with fever, rash, and proteinuria will occur early on. If any of these adverse effects are discovered, D-penicillamine should be stopped and replaced with another medicine. If no other options are available, D-penicillamine-induced side effects may be managed with steroid co-administration.
- D-penicillamine is an immunosuppressant that inhibits collagen cross-linking. Individuals may develop atypical skin and connective tissue collagen after decades of therapy, as well as prolonged depletion of copper and (potentially) other trace metals.
- In the absence of proper clinical evaluation of this therapy approach, D-penicillamine should not be administered in conjunction with zinc.

trientine (chelator): When D-penicillamine is not tolerated, trientine, also known as triethylenetetramine dihydrochloride (2,2,2-tetramine) or trien, is used as a second-line therapy. Because of its efficacy and superior tolerance than D-penicillamine, it is becoming more widely accepted as a first-line treatment; nonetheless, it is not yet widely accessible in all countries. [37]

- All trientine patients should have their complete blood count and urine checked on a regular basis.
- Gastritis with nausea is a rare adverse effect, as is iron deficiency anaemia in situations of overtreatment.
- Trientine should not be used in conjunction with zinc until a thorough evaluation of the combination has been completed. According to recent findings, a combination of trientine and zinc, given at different times during the day such that each treatment is given 5-6 hours apart, may be beneficial in severely decompensated hepatic Wilson disease.

Ammonium TTM:is a chelating medication having anti-angiogenic characteristics that was first used in veterinary therapy to treat copper intoxication. When taken after meals, ammonium TTM binds to the copper in the food, preventing it from being absorbed. It is absorbed into the bloodstream and creates a complex with circulating copper, limiting cellular absorption and resulting in urine excretion if taken on an empty stomach. The recommended dosage is 20 mg three times a day with meals and 20 mg three times a day between meals. The documented negative effects of ammonium TTM include paradoxical worsening, bone marrow suppression, and hepatotoxicity due to its severe chelating properties.However, as compared to trientine, the possibility for neurological degeneration and adverse effects is said to be lower. Ammonium TTM is currently unavailable in India and many other countries. By week 24 of therapy, 57 percent of patients had improved liver function tests and 72 percent had improved free copper levels, according to ongoing phase-2 multicenter studies using a more stable version of a copper chelator (bischoline TTM [WTX101]). More information on the usage of this medication in the treatment of diverse phenotypes of WD is required. [38]

Hepatic WD treatment via liver transplantation: Durand et al. reported in 2001 that for the great majority of patients (90 percent) presenting with fulminant WD without hepatic encephalopathy (HE) upon admission, early use of DP might prevent LT. Nazer's score (serum bilirubin, international normalised ratio (INR), and serum albumin) was renamed New Wilson's Index in 2006 when two more parameters (AST and white blood cell count) were added to the score (NWI). Nonsurvivable without liver transplantation was linked to a NWI score of less than11.NWI and Pediatric End-Stage Liver Disease/Model for End-Stage Liver Disease were shown to have modest accuracy in predicting outcomes in WD in a research from South India. The authors used regression analysis to create a model that used hepatic encephalopathy and bilirubin to predict the prognosis in a fulminant WD presentation. Fischer et colleagues found three of the six patients with NWI scores that predicted mortality, and two of these three patients lived without a transplant. They warned that the results might not be reliable and that this subgroup needed more research. [38-41]

Conclusion:

There’s no doubt that Wilson disease is one of the most concerning clinical challenges that may face the health care system, the challenge of the disease involves around the asymptomatic nature of it, so most patients being diagnosed into later stages of the disease when already great damage has been occurred, and thus the key to effective treatment is early diagnosis. Family screening of Wilson disease’s patient is a must specially to first- and second-degree relatives, because there a high chance of existence of another genetic carriers in the family due to he genetic etiological nature of the disease. With that being said we hope in the future of existence of more effective evaluation and treatment options.

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