Wilson’s disease in Asia

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Abstract

Wilson’s disease is an autosomal recessive disorder of copper metabolism. The resultant accumulation of copper primarily damages the liver and brain, resulting in hepatic, neurological and psychiatric symptoms. There have been many recent studies advancing the understanding of Wilson’s disease in Asia. There are indications that the incidence of Wilson’s disease in parts of Asia may be relatively high. Many genetic studies have identified various hot spots in the ATP7B gene in a variety of the Asian populations. Screening of these hotspot mutations may thus be useful in confirming the diagnosis. Despite the advances in treatment, lack of familiarity by the health care profession resulting in late diagnosis, and poor access to treatment particularly among those from the developing economies remain areas of major concern.

INTRODUCTION

Wilson’s disease (WD) is an autosomal recessive disorder of copper metabolism. The resultant accumulation of copper primarily damages the liver and brain, resulting in hepatic, neurological and psychiatric symptoms. WD is estimated to affect approximately 1 in 30,000 individuals globally. There has been significant recent advances on the understanding and treatment of WA, including the many studies conducted in Asia. Although WA is still not curable, there have been advances in treatment to help control and improve the patients’ condition. In the authors’ experience, many Neurologists in Asia are still not adequately familiar with the disease, and skilled in its modern diagnosis and treatment. In this article, we would like to review the recent advances of the epidemiology, clinical profile, pathogenesis and management of WD, with particular reference to Asia.

EPIDEMIOLOGY

As the country which has the second largest population in the world, there have been a number of studies from India that throw light on WD. Although there is to-date no community-based incidence and prevalence in India, it has been reported that about 15-20 new cases of WD are registered annually at WD specialty clinic in the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, a major neurological center in South India. Taly et al. from NIMHANS presented a cohort of 282 Indian patients with WD which was the largest series of WD in the medical literature. Contrary to the general belief, the disease may manifest even in the fifth or sixth decade. More than two-thirds of patients were males and the authors pointed out Indian males were more likely to be brought for medical attention. It is interesting to note that in South India, where consanguineous marriage is a common practice, close to half of the patients had family history of consanguinity. Consanguineous marriage is known to increase the incidence of recessive disease.

WD is thought to be one of the most common autosomal recessive disorders in Korean. Park et al. determined the carrier frequencies of the three most common mutations associated with WD in Korean. Based on the study, the presumed prevalence of WD is approximately one in 3,000, many times higher than the global prevalence. However, in another Korean study, also by investigating the common mutation prevalence, the frequency of WD was estimated to be is 1/30,778. Thus, the exact incidence of WD in the Korean population has not yet to be determined.
but it may be high. Lin et al. have confirmed the 10 different hotspot mutations in 50 normal Taiwanese individual and estimated a high carrier frequency of WD in the Taiwanese population of about 0.03. It should be noted that the authors have accessed high-resolution melting (HRM) analysis method, which is believed to be feasible and economically beneficial in mutation scanning. The carrier rate of R778L in Hong Kong Han Chinese was estimated to be one in 220, and the frequency of WD was one in 5,400, again indicating a high incidence. There are thus indications that the incidence of WA in parts of Asia may be high.

CLINICAL PROFILE

As Taly et al. from South India have reported, 205 (72.6%) Indian patients had neurologic features, while 52 (18.4%) had hepatic presentation. There were neurologic, psychiatric, hepato-neurologic, and osseomuscular subtypes. Wadia and Dastur pointed out that in the Indian subcontinent, musculoskeletal subtype might be more common. Among neurologic symptoms of Taly et al.’s series, parkinsonism (167, 62.3%), dystonia (95, 35.4%) and ataxia (75, 27.9%) were the three leading problems and the prevalence of seizures was 7.5%. Of the 263 patients where data regarding Kayser-Fleischer (KF) rings was available, 251 (95%) have slit lamp-confirmed KF rings. Five of 37 (14%) patients with hepatic subtype and 7 of 15 (47%) presymptomatic cases did not have KF rings. Taly et al. also reported significant proportions of their patients that were lost to follow up and did not improve. Tatsumi et al. reported 26 patients with WD diagnosed over 8 years from Central Japan. Of the patients, 22 had hepatic form, 5 had neurologic form and 3 had hemolysis. KF rings was present in 15 patients (50%), and in all patients with neurologic involvement. It may be concluded that the clinical profile of WD in Asia is largely similar to elsewhere, and follow up may be poor in some of the developing countries.

PATHOGENESIS

Sinha et al. from South India detected increased levels of serum malondialdehyde (MDA), indicating oxidative damage in 50%, and reduced serum tocopherol level, a naturally occurring antioxidant, in 59% of their Indian patients. In another study to ascertain the role of various cytokines (IL-2, IL-4, IL-6, IFN-γ, TNF-α) in patients with WD, it was noted that both the pro- and anti-inflammatory cytokines are significantly elevated. Meenakshi-Sundaram et al. reported all kinds of lesions in WD. The authors emphasized that the lenticular involvement in WD was not universal as believed, and pathological involvement was far more diffuse in character. Ceruloplasmin is the major ferroxidase in the serum and is essential for iron efflux. The main lesions of WD are not copper overload but rather iron toxicity in the brain and liver, resulting in middle-age onset dementia. In Hayashi’s study, iron and copper were observed in the livers in all 10 patients. Iron overload might be worsened after treatment. Using transmission electron microscopy (TEM) with energy dispersive X-Ray fluorescence spectrometer (EDX) on the liver specimen fixed with 0.1% osmium solution for 45 minutes and embedded in an epoxy resin, different ultrastructures of copper-rich and iron-rich matrices were visualized in the hepatocellular lipofuscin particles. ATP7B is believed to be involved in multi-drug resistance and drug transport. In Nakagawa’s study, ATP7B mRNA and protein expression levels in the cisplatin-resistant xenografts were significantly higher than those in the cisplatin-sensitive xenografts, suggesting that ATP7B was a cisplatin-resistance marker in human non-small cell lung cancers.

GENETIC

The discovery of the ATP7B gene has opened up a new molecular diagnostic approach, and could form the basis of genetic therapy in the future. In East Asia including mainland China, Taiwan, Hong Kong, Korea and Japan, R778L within ATP7B is a hotspot (Table 1). We previously reported seven novel mutations including –36C→T, p.W650X (c.1850G > A), 2810delT, p.Q914X (c.2740C > T), p.T935M (c.2804C > T), p.R1041P (c.3122G > C) and p.E1173K (c.3517G > A) in a cohort of 84 Chinese patients, and p.R778L (c.2333G > T) and p.T935M (c.2804C > T) were hotspots representing 37.7% and 10.0% of patients. We also reported p.P992L (c.2975C > T) as a hotspot and p.Q511X (c.1531C > T) as a novel mutation in the mainland Chinese population. The ninth novel mutation we reported was p.G1268R (c.3802G > A). In addition, we were the first to report that p.R778L (c.2333G > T) was associated with severe phenotype of WD. Hui is the fourth largest ethnic group in China and believed to have some Middle Eastern and Central Asian descent, but ATP7B mutations have seldom been found in Hui patients with WD. There was only one Hui
A patient with homozygous p.R778L (c.2333G > T) being reported. Most of ATP7B mutations detected in Taiwanese WD patients were located in exons 8, 11, 12, 13, 16, 17 and 18. The p.R778L (c.2333G > T) was reported to have high allele frequency (20–35%).

Forty-two different mutations across 16 exons of ATP7B were identified in 65 unrelated Hong Kong Chinese WD patients and 17 were novel. The four most common mutations were p.R778L (c.2333G > T) (17.3%), p.P992L (c.2975C > T) (13.4%), p.I1148T (c.3443 T > C) (8.7%) and p.T1178A (c.3532 A > G) (5.5%). However, p.I1148T (c.3443 T > C) was a polymorphism rather than a mutation. The four most common ATP7B mutations in Korea reported were p.R778L (c.2333G > T), p.A874V (c.2621C > T), p.L1083F (c.3247 C > T) and p.N1270S (c.3809 A > G), accounting for 55.4% of WD patients.

In an Indian study, a total of 51 ATP7B mutations have been documented including 34 novel mutations. Gene screening has been conducted in different parts of India. A total of 33 WD patients and their family members from North West states of India were examined. The p.R778L (c.2333G > T), p.Arg778Gln (c.2333G > A) and p.H1069Q (c.3207C > A) were absent, while p.R778W (c.2332C > T) and p.I1102T (c.3306C > T) accounted for 36%. No significant difference was observed in copper stimulated ATPase activity and liver copper between homozygous and compound heterozygous patients. Serum ceruloplasmin, serum copper levels were significantly lower in homozygous WD patients than that of compound heterozygous. Patients affected with p.R778W (c.2332C > T) showed markedly decreased in ATPase activity than those with p.I1102T (c.3306C > T).

### Table 1: Common ATP7B mutations in different populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Mutation</th>
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<tbody>
<tr>
<td>Chinese (mainland)</td>
<td>p.R778L (c.2333G &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.P992L (c.2975C &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.T935M (c.2804C &gt; T)</td>
</tr>
<tr>
<td>Chinese (Taiwan)</td>
<td>p.R778L (c.2333G &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.Arg778Gln (c.2333G &gt; A)</td>
</tr>
<tr>
<td>Chinese (Hong Kong)</td>
<td>p.R778L (c.2333G &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.P992L (c.2975C &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.T1178A (c.3532 A &gt; G)</td>
</tr>
<tr>
<td>Japanese</td>
<td>p.R778L (c.2333G &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.2871delC</td>
</tr>
<tr>
<td>Korean</td>
<td>p.R778L (c.2333G &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.A874V (c.2621C &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.L1083F (c.3247 C &gt; T)</td>
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<td></td>
<td>p.N1270S (c.3809 A &gt; G)</td>
</tr>
<tr>
<td>Indian (North)</td>
<td>p.R778W (c.2332C &gt; T)</td>
</tr>
<tr>
<td></td>
<td>p.I1102T (c.3306C &gt; T)</td>
</tr>
<tr>
<td>European (North)</td>
<td>p.H1069Q (c. 3207C &gt; A )</td>
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India and their first-degree relatives comprising 400 individuals were studied. Seventeen mutations were identified and 3 were novel including 3412 + 1G > A, p.G591S (c.1771 G > A) and p.T1031A (c.3091 A > G). In the North Indian studies, 24 mutations were identified and 20 of them were novel. In the South Indian population, 20 mutations were reported and 11 were novel.25 There was no single predominant mutation in the Indian population.1

Besides ATP7B, mutations within MURR1, a gene implicated in canine copper toxicosis, is also screened in Asian WD patients. We screened MURR1 mutations in 218 clinically diagnosed patients without ATP7B mutations identified17 and 61 patients with identified ATP7B mutations16, and we did not find any correlation between MURR1 and WD patients. Gupta et al. also screened MURR1 in 109 Indian patients including those with atypical symptoms. They too failed to establish a causal relationship of the MURR1 variant with specific disease phenotype.25 In conclusion, many genetic studies have identified various hot spots in the ATP7B gene in a variety of the Asian populations.

DIAGNOSIS

Laboratory evaluations

In Taly’s series, low serum copper estimation was detected in 75.5% of the 213 Indian patients and low ceruloplasmin levels in 93.1%.2 In a study of copper metabolism in WD patients in North India, there was a good correlation between non-ceruloplasmin bound copper and 24-h urinary copper excretion.26 Ceruloplasmin might be falsely normal in patients with acute presentation especially with hepatic form.1 Park et al. investigated the relationship between biochemical and molecular characteristics in WD patients and found that the rate of mutation detected was associated with ceruloplasmin concentration, suggestive of another mechanism involved in patients with less than two ATP7B mutations.27 However, we feel that those patients with mildly low ceruloplasmin concentrations and without identified ATP7B mutations might not have WD.

Evoked potential

Electrophysiological studies have been done in WD to document any subclinical abnormalities, although they changes are not specific.1 In a study involving 18 Indian WD patients, various evoked potential studies were performed which included motor evoked potential - MEP in 14 patients, somatosensory evoked potential - SEP in 13 patients, auditory brain-stem evoked reaction - ABER in 13 patients and visual evoked potential - VEP in 7 patients. Central motor conduction time (CMCT) was mildly prolonged in 5 (35.7%) patients, tibial nerve SEP was abnormal in 4 (30.8%) patients, and mild to moderate prolongation of P100 latency was noted in VEP of 4 (57%) patients, and ABER was abnormal in 8 (61.5%). Four patients with CMCT prolongation had pyramidal signs. The abnormalities in SEP, VEP and ABER were all subclinical. The number of EP abnormality increased with disease severity.28

Magnetic resonance imaging

In a study of magnetic resonance imaging (MRI) in 100 Indian patients with WD, MRI was abnormal in all the 93 symptomatic patients. The common findings included atrophy of cerebrum, brainstem and cerebellum; signal abnormalities in basal ganglion, midbrain, pons and cerebral white matter. The characteristic “Face of giant panda sign” was seen in 12%.29,30

Genetics screening

As we have mentioned above, R778L (c.2333G > T), P992L (c.2975C > T) and p.T935M (c.2804C > T) are hotspots in Chinese WD patients, which account for nearly 70% of mutations.15,16 Screening for these mutations is highly sensitive and specific for early diagnosis of WD in Chinese population.

MANAGEMENT

Before discussing the specific treatment strategies, it should be stated that there is no consensus regarding therapeutic protocols in Asia. In view of the significant mortality and morbidity of this potentially treatable disease, the non-availability of medications to the poor patients is also a major concern particularly in those areas with developing economies.

Diet

A low-copper diet is essential for WD patients. Foods with high concentrations of copper such as organ meats, shellfish, nuts, mushrooms, and chocolate should be avoided. Copper containers should not be used to prepare or store foods and drinks.
Dimercaprol (BAL)

Dimercaprol (BAL) is the first drug to be introduced in the treatment of WD in India. Dastur et al. did not find any significant improvement in WD patients taking BAL but Sinha et al. reported that all the 8 patients treated with BAL were symptomatically better.1,29

Penicillamine

Penicillamine is the most commonly used de-coppering drug globally, but there is no comprehensive documentation of its use in clinical practice in the Asian populations. A few cases exhibit paradoxical worsening in India.2 Some of the rare adverse events like Steven Johnson syndrome31, myasthenia gravis34 and pseudoxanthoma elasticum35 have been reported. It is generally accepted that long-term use of penicillamine does not cause any clinical, electrophysiological or immunological evidence of myasthenia gravis in WD patients. In one study of 16 patients with 30 successful pregnancies, there was no report of teratogenicity with low dose penicillamine and zinc.36

Trientine

Trientine was introduced as an alternative to penicillamine in 1969 and has few side effects. It is an effective treatment for WD and indicated especially in patients who are intolerant of penicillamine. However, it is not available in Asia.

Zinc

In the first study in India of zinc therapy by Murthy et al., of the 8 patients started on maintenance zinc therapy, 7 had sustained improvement.33 In another study by Sinha et al.36, 45 patients were initially started on both penicillamine and zinc sulfate, but subsequently had to be shifted to zinc as the lone agent due to economic reasons and were followed for the next two and half years. Forty four patients (97.7%) remained status quo or improved marginally. Only one patient reported worsening in dysarthria. There were no adverse effects. By genetic analysis, we identified 17 presymptomatic patients with WD. Prophylactic treatment using zinc was given to 14 over 3 to 5 years. This resulted in decreased level of urinary copper, which indicated effective control of copper metabolism. None of the patients developed clinical symptoms of WD or adverse effects of zinc therapy by the end of the study period. In contrast, 3 patients who refused treatment had symptomatic progression of the disease.37 This was the first study of zinc therapy on presymptomatic WD patients whose diagnosis was confirmed by molecular analysis. In Japan, zinc therapy is not approved for use in WD.

Liver transplantation

Liver transplantation is an effective treatment for fulminant hepatic failure in WD. De-coppering treatment has been proven to be beneficial for WD patients. If chelation therapy fails to suppress the progression of the disease, orthotopic liver transplantation (OLT) is the only alternative treatment. However, the application of OLT for WD is still under investigation, and the therapeutic benefit of OLT on WD is being debated, especially for patients with neuropsychiatric deterioration.38-40 OLT is currently not recommended as a primary treatment for patients with neuropsychiatric symptoms in mainland China.41

CONCLUSIONS

Incidence of WD may be higher in Asia. The diagnosis of WD is usually based on the typical clinical manifestations including finding KF rings by slit-lamp examination, and estimation of serum ceruloplasmin. Screening of hotspot mutations within ATP7B can be used as a confirmatory diagnostic test. Basal ganglion involvements are common in cranial MRI and can help to confirm diagnosis. Evoked potential can document some subclinical abnormalities but the changes are nonspecific. A low-copper diet should be advised as part of treatment. Penicillamine is still the most commonly used de-coppering drug. Trientine is not available in Asia. Zinc monotherapy is effective as presymptomatic treatment, and can also be an alternative drug in maintenance treatment. Liver transplantation is an effective treatment for fulminant hepatic failure in WD. Whether it can improve neurological and psychiatric symptoms is still controversial.

DISCLOSURE

The authors declare that they have no conflicts of interest.

REFERENCES


