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REVIEW ARTICLE

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.[1] 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.[2]

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.[3] However, in another Korean study, also by investigating the common mutation prevalence, the frequency of WD was estimated to be is 1/30,778.[4] Thus, the exact incidence of WD in the Korean population has not yet to be determined,

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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.[5] 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[6], 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.[2] Wadia and Dastur pointed out that in the Indian subcontinent, musculoskeletal subtype might be more common.[7] 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.[2] 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.[8] 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.[9] In another study to ascertain the role of various cytokinesm (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.[10] 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.[11] 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 toxicosis 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.[12] Using transmission electron microscopy (TEM) with energy dispersive X-Ray fluoresence 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.[13] 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.[14]

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.[15] 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.[16] The ninth novel mutation we reported was p.G1268R (c.3802G > A).[17] In addition, we were the first to report that p.R778L (c.2333G > T) was associated with severe phenotype of WD.[15,18] 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

Table 1: Common ATP7B mutations in different populations

Population	Mutation
Chinese (mainland)	p.R778L (c.2333G > T) p.P992L (c.2975C > T) p.T935M (c.2804C > T)
Chinese (Taiwan)	p.R778L (c.2333G > T) p.Arg778Gln (c.2333G > A)
Chinese (Hong Kong)	p.R778L (c.2333G > T) p.P992L (c.2975C > T) p.T1178A (c.3532 A > G)
Japanese	p.R778L (c.2333G > T) p.2871delC
Korean	p.R778L (c.2333G > T) p.A874V (c.2621C > T) p.L1083F (c.3247 C > T) p.N1270S (c.3809 A > G)
Indian (North)	p.R778W (c.2332C > T) p.I1102T (c.3306C > T)
European	p.H1069Q (c. 3207C > A)

patient with homozygous p.R778L (c.2333G > T) being reported.[19] 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) or p.Arg778Gln (c.2333G > A) was reported to have high allele frequency (20–35%).[20] 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%).[6] However, p.I1148T (c.3443 T > C) was a polymorphism rather than a mutation.[21] 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.[3,22] It should be noted that in Kim's study, these mutations were not detected by polymerase chain reaction (PCR) combined to restriction fragment length polymorphism (RFLP) or sequencing, but by SYBR Green I based multiplex analysis, a newly developed method.[4] In central Japan, two major mutations, p.R778L (c.2333G > T) and 2871delC, were identified in a cohort of 26 patients and six novel mutations were also identified.[8] In a cohort of 51 Japanese WD patients, those with truncated *ATP7B* mutations were more prone to fulminant hepatic failure when compared with those with missense mutations (36.4% vs 0).[23]

In an Indian study, a total of 51 *ATP7B* mutations have been documented including 34 novel mutations.[1] 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).[24] In another study, 109 unrelated patients in Eastern

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 identified[17] and 61 patients with identified *ATP7B* mutations[16], 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[31] 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 Inida.[32] Some of the rare adverse events like Steven Johnson syndrome[33], myasthenia gravis[34] and pseudoxanthoma elasticum[35] 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 zince 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

1. Taly AB, Prashanth LK, Sinha S. Wilson's disease: An Indian perspective. *Neurol India* 2009; 57:528-40.
2. Taly AB, Meenakshi-Sundaram S, Sinha S, *et al*. Wilson disease: description of 282 patients evaluated over 3 decades. *Medicine* 2007; 86:112-21.

3. Park HD, Ki CS, Lee SY, *et al*. Carrier frequency of the R778L, A874V, and N1270S mutations in the ATP7B gene in a Korean population. *Clin Genet* 2009; 75:405-7.
4. Kim GH, Yang JY, Park JY, *et al*. Estimation of Wilson's disease incidence and carrier frequency in the Korean population by screening ATP7B major mutations in newborn filter papers using the SYBR green intercalator method based on the amplification refractory mutation system. *Genet Test* 2008; 12:395-9.
5. Lin CW, Er TK, Tsai FJ, *et al*. Development of a high-resolution melting method for the screening of Wilson disease-related ATP7B gene mutations. *Clin Chim Acta* 2010; 411:1223-31.
6. Mak CM, Lam CW, Tam S, *et al*. Mutational analysis of 65 Wilson disease patients in Hong Kong Chinese: Identification of 17 novel mutations and its genetic heterogeneity. *J Hum Genet* 2008; 53:55-63.
7. Wadia NH, Dastur DK. Wilson's disease in four Indian families. *Neurology* (Bombay) 1963; 11:1.
8. Tatsumi Y, Hattori A, Hayashi H, et al. Current state of Wilson disease patients in central Japan. *Inter Med* 2010; 49:809-15.
9. Sinha S, Christopher R, Prashanth LK, *et al*. Malonialdhyde levels in Wilson's disease? *Ann India Acad Neurol* 2004; 7:507-10.
10. Goyal MK, Sinha S, Patil SA, *et al*. Do cytokines have any role in Wilson's disease?. *Clin Exp Immunol* 2008; 154:74-9.
11. Meenakshi-Sundaram S, Mahadevan A, Taly AB, *et al*. Wilson's disease: A clinico-neuropathological autopsy study. *J Clin Neurosci* 2008; 15:409-17.
12. Hayashi H, Yano M, Fujita Y, *et al*. Compound overload of copper and iron in patients with Wilson's disease. *Med Mol Morphol* 2006; 39:121-26.
13. Motonishi S, Hayashi H, Fujita Y, et al. Copper- and iron-rich matrices in hepatocellular lipofuscin particles of a young male patient: diagnostic ultrastructures for Wilson disease. *Ultrastruct Pathol* 2006; 30:409-14.
14. Nakagawa T, Inoue Y, Kodama H, *et al*. Expression of copper-transporting P-type adenosine triphosphatase (ATP7B) correlates with cisplatin resistance in human non-small cell lung cancer xenografts. *Oncol Rep* 2008; 20:265-70.
15. Wu ZY, Wang N, Lin MT, *et al*. Mutation analysis and the correlation between genotype and phenotype of Arg778Leu mutation in Chinese patients with Wilson disease. *Arch Neurol* 2001; 58(6):971-6.
16. Zhao GX, Wu ZY, Chen WJ, *et al*. Mutation analysis of MURRl in Chinese patients with Wilson disease. *Zhonghua Shenjin Ke Za Zhi* 2006; 8:548-51. (in Chinese)
17. Wu ZY, Zhao GX, Chen WJ, *et al*. Mutation analysis of 218 Chinese patients with Wilson disease revealed no correlation between the canine copper toxicosis gene MURR1 and Wilson disease. *J Mol Med* 2006; 84:438-42.
18. Wu ZY, Wang N, Lin MT, *et al*. Genotype-phenotype correlation of patients with wilson disease in Chinese population. *Zhonghua Yi Xue Za Zhi* 2003; 83:309-15. (in Chinese)
19. Gu YH, Kodama H, Du SL, *et al*. Mutation spectrum and polymorphisms in ATP7B identified on direct sequencing of all exons in Chinese Han and Hui ethnic patients with Wilson's disease. *Clin Genet* 2003; 64:479-84.
20. Wan L, Tsai CH, Tsai Y, *et al*. Mutation analysis of Taiwanese Wilson disease patients. *Biochem Biophys Res Commu* 2006; 345:734-8.
21. Wu ZY, Wang N, Lin MT, *et al*. Detection and analysis of mutations in Chinese patients with Wilson disease. *Zhonghua Shenjin Ke Za Zhi* 2001; 34:152-5. (in Chinese)
22. Yoo HW. Identification of novel mutations and the three most common mutations in the human ATP7B gene of Korean patients with Wilson disease. *Genet Med* 2002; 4: 43S-48S.
23. Okada T, Shiono Y, Kaneko Y, *et al*. High prevalence of fulminant hepatic failure among patients with mutant alleles for truncation of ATP7B in Wilson's disease. *Scand J Gastroenterol* 2010; 45:1232-7.
24. Kumar S, Thapa B, Kaur G, *et al*. Analysis of most common mutations R778G, R778L, R778W, I1102T and H1069Q in Indian Wilson disease patients: correlation between genotype/phenotype/copper ATPase activity. *Mol Cell Biochem* 2007; 294:1-10.
25. Gupta A, Chattopadhyay I, Dey S, *et al*. Molecular pathogenesis of Wilson disease among Indians: a perspective on mutation spectrum in ATP7B gene, prevalent defects, clinical heterogeneity and implication towards diagnosis. *Cell Mol Neurobiol* 2007; 27:1023-33.
26. Prasad R, Kaur G, Walia BN. A critical evaluation of copper metabolism in Indian Wilson's disease children with special reference to their phenotypes and relatives. *Biol Trace Elem Res* 1998; 65:153-65.
27. Park HD, Park HK, Chung HS, *et al*. Association of ATP7B mutation detection rate with biochemical characteristics in Korean patients with Wilson disease. *Ann Clin Lab Sci* 2010; 40:15-9.
28. Das M, Misra UK, Kalita J. A study of clinical, MRI and multimodality evoked potentials in neurologic Wilson disease. *Eur J Neurol* 2007; 14:498-504.
29. Sinha S, Taly AB, Ravishankar S, *et al*. Wilson's disease: cranial MRI observations and clinical correlation. *Neuroradiology* 2006; 48:613-21.
30. Thapa R, Ghosh A. Face of the giant panda' sign in Wilson disease. *Pediatr Radiol* 2008; 38:1355.
31. Dastur DK, Manghani DK, Wadia NH. Wilson's disease in India. I. Geographic, genetic, and clinical aspects in 16 families. *Neurology* 1968; 18 (1 Pt 1): 21-31.
32. Brewer GJ, Terry CA, Aisen AM, *et al*. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. *Arch Neurol* 1987; 44:490-3.
33. Murthy BS, Murthy JM, Krishnaveni A, *et al*. Wilson's disease in south India and experience with zinc therapy. *J Assoc Physicians India* 1988; 36: 417-9.
34. Narayanan CS, Behari M. Generalized myasthenia gravis following use of D-pencillamine in Wilson's disease. *J Assoc Physicians India* 1999; 47:648.

35. Pal PK, Sinha S, Pillai S, *et al*. Successful treatment of tremor in Wilson's disease by thalamotomy: A case report. *Mov Disord* 2007; 217:37-40.
36. Sinha S, Taly AB. Withdrawal of penicillamine from zinc sulphate–penicillamine maintenance therapy in Wilson's disease: promising, safe and cheap. *J Neurol Sci* 2008; 264:129-32.
37. Wu ZY, Lin MT, Murong SX, *et al*. Molecular diagnosis and prophylactic therapy for presymptomatic Chinese patients with Wilson disease. *Arch Neurol* 2003; 60:737-41.
38. Medici V, Mirante VG, Fassati LR, *et al*. Monotematica AISF 2000 OLT Study Group. Liver transplantation for Wilson's disease: The burden of neurological and psychiatric disorders. *Liver Transpl* 2005; 11:1056-63.
39. Senzolo M, Loreno M, Fagiuoli S, *et al*. Different neurological outcome of liver transplantation for Wilson's disease in two homozygotic twins. *Clin Neurol Neurosurg* 2007; 109:71-5.
40. Litwin T, Gromadzka G, Członkowska A. Neurological presentation of Wilson's disease in a patient after liver transplantation. *Mov Disord* 2008; 23:743-6.
41. Liang XL, Yang RM, Wu ZY, Wang N, Li XH, Wang X. Guidelines on diagnosis and treatment of Wilson's disease. *Zhonghua Shenjing Ke Za Zhi* 2008; 41:566-9.