Polyneuropathy associated with Wilson's disease

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Wilson's disease, named after S.A.K. Wilson, who first described the disease in 1912, is a genetic disorder of copper metabolism. It is transmitted by autosomal recessive inheritance and is characterized by impaired copper extraction in the bile.[1] The clinical manifestations of Wilson's disease develop, most probably as a result of excessive accumulation of copper in various organ systems, particularly the liver and brain. The worldwide prevalence rate of Wilson's disease is 1:30,000, but it increases where consanguinity is common. Recognition of Wilson's disease is sometimes difficult because of its diverse manifestations. Peripheral neuropathy is rarely reported in the context of Wilson's disease.[2] Here, we present the electrophysiological and pathological findings of a patient with peripheral neuropathy who was on therapy for Wilson's disease for 4 years.

An 18-year-old man was admitted with complaints of paresthesia in his upper and lower limbs present for 3-4 years, disturbing mostly in the last 3 months and during the evening hours. He had a history of Wilson's disease diagnosed 4 years ago according to the following criteria; low serum ceruloplasmin, abnormal serum copper and urinary copper excretion, and Kayser-Fleischer ring. His nephew had died because of chronic hepatic disease of unknown origin in the first decade, and there was no other disease history in the family. He had taken metalcaptase and zinc for 3 years and was still taking trientine for 7 months. Physical examination on admission was normal (weight: 57 kg, height: 174 cm). On neurological examination, deep tendon reflexes were abolished and vibration sensation was absent in the lower limbs prominent on the left. Other examination findings were normal, and ataxia, tremor, or gait abnormalities were not noted. Liver biopsy performed 4 years ago was compatible with hepatic cirrhosis and serological markers for hepatitis were negative. Glucose, vitamin B12, folate, and thyroid function tests were within normal limits. In the last laboratory tests, total blood count was normal, serum glutamate oxaloacetate transaminase: 61 IU/L (reference range (RR): 10-42 IU/L), serum glutamate pyruvate transaminase: 69 IU/L (RR: 10-60), alkaline phosphatase: 248 IU/L (RR: 25-100), gamma-glutamyl transferase: 431 IU/L (RR: 7-60), total bilirubin: 1.51 mg/dl (RR: 0.4-1.35), direct bilirubin: 0.54 mg/dl (RR: 0.1-0.5), and serum copper level: 81 µg/dl (RR: 80-155). Cerebral MRI did not show any pathological findings. A nerve conduction study was performed using standard techniques of surface stimulation and recording. Skin temperature was maintained higher than 32^0C. Electroneurographic examination revealed sensorimotor polyneuropathy associated with axonal degeneration prominent in the lower limbs. Distal motor latency, F-wave latency, motor nerve conduction velocity, and compound motor action potential were measured in the median, ulnar, peroneal, and posterior tibial nerves, and H reflex in the posterior tibial nerves. Sensory nerve conduction velocity and sensory nerve action potential were obtained in the median, ulnar, radial, and sural nerves. Distal motor latencies were prolonged in most motor nerves. F latencies in upper limbs were prolonged, and inexcitable in lower limbs, and H reflex was prolonged bilaterally. Motor nerve conduction velocities were inexcitable in the lower limbs. Sensory nerve action potentials were decreased (**Table 1**). Electromyography showed fibrillation and positive sharp waves, neurogenic motor unit potentials, or absence of voluntary activity in the extensor digitorum brevis and abductor hallucis muscles. Biopsy from nervus peroneus superficialis was performed and specimens, painted by paraffin and toluidine blue, were prepared from biopsy samples. Hematoxylin eosin, Bielschowsky reticulin, myelin, and crystal violet, special histochemical paints were applied to paraffin sections and examined by light microscope. Histochemical examination showed loss of myelinated axons and slimmed myelin sheath around axons. The endoneural capillary walls did not reveal any changes (**Figure 1**).

Wilson's disease is a systemic illness of protean presentation related to an abnormality of copper metabolism.[1] In the initial asymptomatic stage, copper accumulates in the hepatic cytosol and after the cytosols are saturated, copper accumulates in hepatic lysosomes and spills into the circulation. By the continued release of copper into the blood, chronic neurological, hepatic, and renal disease may develop gradually.[1] Typically, patients present with psychiatric, neurological, or hepatic symptoms during the second to fourth decades of life. One-third of the patients present with liver disease, one-third with neurologic features, and one-third with psychiatric features.[3] Neurological manifestations are rare before the age of 10, but when present, dystonia is the most common symptom.[4] Neurological Wilson's disease usually develops in the second or third decade of life and the mean age of onset for neurological symptoms is 21 years. Initial symptoms may be subtle, such as abnormal behavior and deteriorating performance at school. Our patient could only complete primary school, and his performance was not good. More prominent neurological findings that subsequently develop are dysdiadochokinesia, dysarthria, bradykinesia, tremor, ataxia, chorea, and hypersalivation. According to the MRI of brain, 3 distinct subsets of patients with Wilson's

Table 1 - Electroneurography results.

Nerves			Nerve intervals				
Side	Motor/ Sensory	Nerve	Terminal latency DL	F	Interval (cm)	Conduction time (m/sn)	Amp. mV/μV
L	M	Median (abductor pollicis brevis)	4.48	32.9	8.0	53.5	15
L	M	Ulnaris (abductor digitorum minimus)	3.52	34.9	7.0	50.0	14
R	M	Median (abductor pollicis brevis)	4.60	34.5	8.0	55.2	15
R	M	Ulnaris (abductor digitorum minimus)	3.92	35.3	8.0	56.3	14
R	M	Musculocutaneus (Erb-biceps)	3.60		31.0		4
R	M	Radialis (Erb-triceps)	2.80		8.0		4
L	M	Musculocutaneus (Erb-biceps)	4.50		30.5		5
R	S	Ulnaris (5. finger-wrist)	3.16		16.5	54.1	2.2
R	S	Median (2. finger-wrist)	3.52		19.3	54.5	4.2
R	S	Radial (1. finger-wrist)	3.18		16.5	51.9	4.9
L	S	Median (2. finger-wrist)	3.22		16.8	52.2	3
L	S	Ulnaris (5. finger-wrist)	3.02		16.4	54.3	7.8
L	S	Radial (1. finger-wrist)	3.28		16.4	50.0	5
R	M	Tibialis (abductor hallucis)		Absent		Inexcitable	
R	M	Peroneal (extensor digitorum brevis)		Absent		Inexcitable	
R	M	Peroneal (capitulum fibula-tibialis anterior)	5.79		18.5		3.2
L	M	Peroneal (extensor digitorum brevis		Absent		Inexcitable	
L	M	Tibialis (abductor hallucis)		Absent		Inexcitable	
L	S	Suralis	4.00	-	18.0	45.0	4
R	S	Suralis	4.12	-	16.8	40.8	3

L - left, R - right, S - sensory, M - motor, DL - distal latency, F - F response, Amp - amplitude

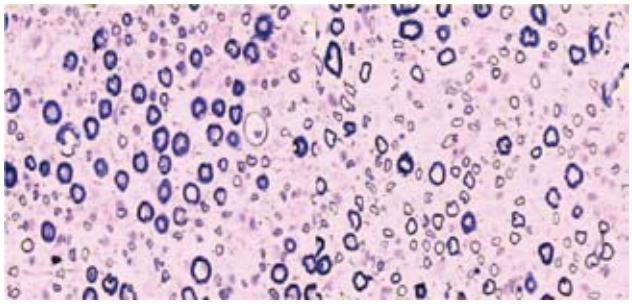

Figure 1 - Axonal degeneration of nervus tibialis superficialis specimen.

disease have been described: pseudoparkinsonian, pseudosclerosis, and dyskinesia. Our patient did not have these symptoms. Peripheral neuropathy is very rarely reported in the context of Wilson's disease. Neuropathy may be the initial symptom of Wilson's disease or may be determined during the follow-up of the disease.[3] Moreover, drugs such as penicillamine used for the treatment of any other chronic liver disease or metabolic disorders (axonal or demyelinating) may cause polyneuropathy, characteristic features similar to Wilson's disease.[5] In our patient, polyneuropathy was diagnosed in the fourth year of the disease, however his symptoms associated with polyneuropathy had started at approximately the same time as the beginning of Wilson's disease. Also, his symptoms had progressively increased. There is a reported case, whose initial symptoms were associated with polyneuropathy and diagnosed as Wilson's disease during the follow-up, and the signs and symptoms of polyneuropathy were improved by treatment of Wilson's disease with penicillamine. Because of the existence of polyneuropathy before the use of penicillamine, this drug was not thought as an etilogy.[2] Our patient did not take penicillamine, and although the disease was being treated, polyneuropathy symptoms had progressed and at the time of diagnosis by us, the polyneuropathy level was severe. Pathological studies in the reported cases with Wilson's disease and polyneuropathy had showed axonal degeneration of the peripheral nerves or varied degrees of destruction of the myelin sheath associated with axonal damage.[2] In our patient, electrophysiological examination was compatible with sensorimotor polyneuropathy associated with axonal degeneration prominent in the lower limbs and pathological examination showed loss of myelinated axons and slimmed myelin sheath around axons.

Our patient is a case of Wilson's disease in which polyneuropathy symptoms started at the beginning of the disease and was diagnosed in the fourth year with severe electrophysiological and pathological findings. Although the disease was being treated (not

penicillamine) and the clinical course was stable, polyneuropathy progressed. Because of the rarity of reported Wilson's disease with polyneuropathy in the literature, further studies are needed to explain the mechanism of abnormal copper metabolism, and the necessary period for causing neuropathy.

Received 20th March 2007. Accepted 30th May 2007.

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