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Characteristics of neurological Wilson's disease without Kayser–Fleischer ring

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ABSTRACT

Background: Although Kayser–Fleischer ring has been regarded as a key diagnostic feature of neurologic Wilson's disease, there have been previous reports of neurologic Wilson's disease patients without Kayser–Fleischer ring. We assessed the characteristics of neurologic Wilson's disease patients without Kayser–Fleischer ring.
Methods: We enrolled neurologic Wilson's disease patients from 4 university hospitals by review of medical records in this study. Patients with neurologic Wilson's disease were diagnosed based on the neurologic symptoms and international scoring system for the diagnosis of Wilson's disease. All subjects were divided into two groups according to the presence of a Kayser–Fleischer ring. We compared demographic data, laboratory findings and imaging findings of the liver and brain between the two groups.
Results: There were 12 (26.7%) patients without Kayser–Fleischer ring out of a total of 45 neurologic Wilson's disease patients. The Wilson's disease patients without Kayser–Fleischer ring demonstrated a higher ceruloplasmin concentration and serum copper level than those with Kayser–Fleischer ring. In addition, liver cirrhosis and typical signal changes in brain magnetic resonance imaging were less common in neurologic Wilson's disease patients without Kayser–Fleischer ring.
Conclusion: Based on our results, the absence of Kayser–Fleischer ring can be regarded as a form of neurologic Wilson's disease with less copper involvement. In addition, it is important to understand these features and to perform further investigations if patients without Kayser–Fleischer ring are suspected of having neurologic Wilson's disease.

1. Introduction

Wilson's disease (WD) is an inherited disorder of abnormal copper deposition in multiple organs, including the brain [1], and is associated with heterogeneous mutations in the adenosine triphosphatase 7B gene (ATP7B) [2]. Although WD can have highly variable clinical presentations, hepatic and neurological symptoms are the main clinical features of WD, and about half of WD patients present with neurologic symptoms [3–5]. Patients with WD require lifelong treatment, because interruption of therapy or inadequate treatment can lead to death within 9 months to 3 years [6], whereas appropriate treatment can result in stability or improvement of symptoms [7]. Based on these previous studies, it is clear that early and correct diagnosis of WD is indispensable.

Among various clinical presentations of WD, the presence of a KF ring has been regarded as a key diagnostic feature for neurologic WD, because a KF ring was believed to be present in almost all patients with neurologic WD [8], in spite of presentation of a KF ring in less than half of the patients with hepatic WD [3,9]. However, there have been some case reports of neurologic WD patients without KF ring [10–13], and previous studies have reported that only 77.8–85.2% of neurologic WD patients show a KF ring [3,14,15]. Despite these studies, little is known about the clinical and laboratory characteristics of neurologic WD without KF ring and as far as we know, there has been no study focusing solely on neurologic WD patients without KF ring.

Thus, we conducted the present study comparing neurologic WD patients with KF ring to those without KF ring to elucidate the characteristics of neurologic WD patients without KF ring and to help physicians diagnose these patients earlier.

2. Methods

2.1. Subjects

Forty-five patients with neurologic WD who were diagnosed at the Department of Neurology in four university-based hospitals

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Table 1
Inclusion criteria of neurologic WD.

(i) Neurologic symptoms or signs
(ii) Score of 4 or more in an international scoring system for the diagnosis of WD
(iii) Typical abnormality of copper metabolism (low serum ceruloplasmin level <14 mg/dl and increased 24 h urine copper excretion >76 μg/day)
(iv) Family history of WD (within first-degree relative) or typical signal change on brain MRI
(v) Positive ATP7B gene mutation analysis (homozygote or compound heterozygote)
(vi) Increased hepatic copper content (>250 μg/g)

Subjects who meet (i), (ii) and at least one among the others (iii–vi) were defined as the patients with neurologic WD.
WD, Wilson's disease; MRI, magnetic resonance imaging; ATP7B, adenosine triphosphatase 7B.

(Samsung Medical Center, Yonsei University Medical Center, Boramae Medical Center, and Hanyang University Medical Center) in Seoul, Korea, from 1995 to 2011, were enrolled in this study. We reviewed the clinical and laboratory data of these patients retrospectively.

Because there was no consensus on the diagnostic criteria of WD, we defined neurologic WD patients by strict inclusion criteria based on previous literature [6,8,16–18]. Inclusion criteria were shown in Table 1. In addition, to avoid contamination from patients with hepatobiliary disease resulting in the abnormality of copper metabolism, we excluded patients with hepatobiliary disease except liver cirrhosis (LC) on liver computed tomography (CT) or sonography.

The KF ring was examined using a slit lamp by an ophthalmologist in each hospital. To confirm the absence of the KF ring, two different ophthalmologists checked for the KF ring in the case of patients without KF ring. Based on the presence of the KF ring at the initial visit without chelating medication, all subjects were divided into two groups: neurologic WD patients with KF ring and neurologic WD patients without KF ring (KF (+) group and KF (−) group, respectively).

Demographic data, including age, sex, and onset age of neurologic symptoms, were collected. Neurologic symptoms of all subjects were divided into 4 subtypes: Parkinsonism, tremor and predominant dysarthria (pseudo-sclerosis), dystonia, and chorea [19]. Serum ceruloplasmin, serum copper, 24 h urinary copper, and liver function tests (LFT, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma glutamyl transferase) were checked.

Liver CT or sonography, was performed in all subjects to confirm LC. LC was defined as typical abnormalities on liver computed tomography or sonography. Brain MRI was performed in 41 of the 45 subjects, and typical signal changes in brain MRI were defined as bilateral signal changes of the basal ganglia, thalamus, or midbrain, based on previous studies [20,21]. ATP7B gene mutation analysis was done in 19 subjects, penicillamine challenge test (PCT) in 9 subjects, and copper quantification in dry liver tissue after liver biopsy in 4 subjects.

ATP7B gene mutation analysis was done using polymerase chain reaction sequencing to investigate molecular defects. Mutation screening was performed for 3 exons (8, 11 and 18) until 2004 and 7 exons (8, 10, 11, 14, 15, 16 and 18) from 2004 onwards. These exons represent the most common mutations in Korean patients with WD [22,23]. Subjects with positive ATP7B gene mutation were defined as the subjects with a homozygote or compound heterozygote gene mutation. The study received approval from the institutional review board of each involved hospital.

2.2. Statistical analysis

All data are presented as the median (interquartile range). Differences between two groups were evaluated using the unpaired Student's *t*-test or the Mann–Whitney *U* test for continuous and ordinal variables, and Pearson's chi-square test or Fisher's exact test was used to analyze categorical variables. p-Values of <0.05 were considered statistically significant. All statistical analyses were conducted using commercially available software (SPSS for Windows, version 15.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic data

Out of the 45 patients with neurologic WD, 33 subjects presented with KF ring (73.3%), and 12 subjects presented without KF ring. All the laboratory and clinical data of neurologic WD patients without KF ring are shown in Table 2. The median age of the whole subjects with neurologic WD was 33.0 (28.0–39.5), and 29 subjects were male (64.4%). The median age of onset of neurologic symptom was 21.0 (18.0–28.0) years, and the median levels of serum ceruloplasmin, copper, and 24 h urine copper were 2.5 (2–10.1) mg/dl, 30.4 (23.0–51.0) μg/dl, and 208.7 (135.7–397.1) μg, respectively. Clinically, subjects demonstrated pseudo-sclerosis (91.1%), Parkinsonism (42.2%), dystonia (24.4%), and chorea (2.2%). Positive MRI findings were found in 27 (65.9%) of 41 neurologic WD patients who underwent brain MRI. MRI signal changes were observed in the basal ganglia (20 subjects, 74.1%), midbrain (15 subjects, 55.6%), and thalamus (12 subjects, 44.4%). Twenty-six subjects (57.8%) showed liver cirrhosis on computed tomography or sonography. Gene mutations were detected in 8 (42.1%) of 19 neurologic WD patients who were tested for ATP7B gene mutation analysis.

3.2. Clinical features of neurologic WD patients without KF ring

In terms of demographic data and clinical symptoms, no significant difference was observed between the KF (+) group and the KF (−) group (Table 3). Although the KF (−) group showed delayed

Table 2
Laboratory data of the KF (−) group.

#	Sex/age	Ceru	S–Cu	U–Cu	ATP7B gene test	PCT	LC	MRI	Symptoms	Other laboratory data
1	F/28	2	18.8	111.9					Park	Hepatic copper content 2260 μg/g
2	M/30	33.8	86	74					PS, Park	Hepatic copper content 787 μg/g
3	M/25	7.3	29	245.3		+			PS	
4	M/38	6.5	28	50	p.Asn1270Ser, p.Val1109Met (compound heterozygote)				PS, Park	
5	F/28	14.6	52	162.5			+	+	PS, seizure	
6	M/26	25.3	75.8	294	Ile929Val (homozygote)				PS, dyst	
7	F/30	19.5	101.5	384.7			+		PS, Park, dyst	WD family history (sister)
8	M/27	18.2	82.1	893.7	p.Asn1270Ser (homozygote)				PS	
9	M/37	2	50	164				+	PS, dyst, cog	
10	M/32	12.9	69	493					PS	Improved after penicillamine medication
11	M/34	0.1	24.9	178.55	p.Arg778Leu (homozygote)			+	PS	Liver tissue, rhodamine staining (+)
12	M/43	20	46.2	17.4		+		+	PS, ataxia, cog	Hepatic copper content 276.4 μg/g

KF, Kayser–Fleischer; Ceru, ceruloplasmin; S–Cu, serum copper; U–Cu, 24 h urine copper; PCT, penicillamine challenge test; Park, Parkinsonism; PS, pseudo-sclerosis; dyst, Dystonia; cog, cognitive impairment. Normal range: Ceru, 20–60 mg/dl; S–Cu, 55–150 μg/dl; U–Cu, <38 μg/day.