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Neurological features and management of Wilson disease in children: an evaluation of 12 cases

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Abstract

Aim: Wilson's disease is an autosomal recessive disorder of copper metabolism which leads to copper overload in different tissues of the body. The aim of this study was to present the neurologic features of Wilson's disease and to assess the clinical course of neurological findings in children receiving anti-copper treatment.

Material and Methods: Twelve children with a diagnosis of Wilson's disease and findings of central nervous system involvement who were followed up in the Department of Pediatric Neurology and Pediatric Gastroenterology of the School of Medicine at Erciyes University were enrolled in the study.

Results: The study cases consisted of five boys (42%) and seven girls (58%). The mean age at the time of diagnosis was 9.9±3.4 years (5-15 years). The mean duration of follow-up was 49.0±36.4 months (15-128 months). Neurological findings at presentation included headache in seven cases (58%), tremor in seven cases (58%), dystonia in three cases (25%), ataxia in two cases (17%), dizziness in two cases (17%), numbness in the hands and acute weakness in one case (8%) and syncope in one case (8%). Headache, dizziness, syncope, numbness in hands and acute weakness symptoms resolved completely within six months after receiving treatment. Movement disorders either decreased or remained stable in seven of the eight cases. However, one patient developed progressively worsening dystonia despite to all treatments.

Conclusions: Wilson's disease can be manifested with signs and symptoms of central nervous system in the childhood. Wilson's disease should be considered in all children presenting with movement disorders. A complete neurological assessment should be carried out in all cases with Wilson's disease. (Turk Pediatri Ars 2016; 51: 15-21)

Keywords: Children, movement disorders, neurotoxicity, Wilson's disease

Introduction

Wilson's disease (WD) is an autosomal recessive disorder which occurs as a result of disorder of copper metabolism. The disorder of metabolism in patients with WD develops as a result of mutations in the adenosine triphosphatase 7B gene (ATP7B) located on the long arm of the 13th chromosome (1). Copper leads to tissue damage by accumulating in many organs including mainly the liver and brain as a result of lack of production of the proteins responsible of excretion of copper into the bile ducts in relation with these mutations. The incidence of WD is considered to be about 1/30 0000 (2). Although the clinical findings of the disease depend on the organ involved, they are usually related with involvement of the liver or central nervous system. Although clinical and laboratory findings related with hepatic involvement are observed more commonly, neurological symptoms are present in approximately 15% of the children (3). The findings occuring as a result of brain involvement are almost always limited to the motor system and typically involve movement disorders. The main movement disorders include dystonia, tremor, ataxia and loss of motor control. Dystonia is characterized with mask-like face, rigitidy, gait disorder and pseudobulbar involvement (dysarthria, dysphagia, hypersalivation etc.) (2-4). "Kayser-Fleischer (KF) ring" which is a marked brown-green discoloration around the cornea related with accumulation of copper in the "descement's" membrane of the cornea is a significant finding of WD. Presence of KF ring on opthalmologic examination or detection of mutations in the ATP7B gene support the diagnosis. The diagnosis is based on laboratory findings including reduced serum ceruloplasmin level in association with increased 24-hour urine copper, serum free copper and hepatic tissue copper (2, 5). Low copper diet, D-penicillamine, triethylentetramine, amonium tetratiomolibdate and

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zinc are used in treatment (2-4). In this study, the clinical features of WD patients who presented with neurological findings or who developed neurological findings during the follow-up period are presented.

Material and Methods

Among 69 patients who were being followed up with a diagnosis of WD in the Division of Pediatric Gastroenterology in Erciyes University School of Medicine, a total of 12 patients including nine patients who developed neurological findings during the follow-up period and started to be followed up in the Division of Pediatric Neurology in Erciyes University Medical Faculty and three patients who presented to the Division of Pediatric Neurology with neurological findings and were diagnosed with WD were included in this study. The study was approved by Erciyes University Local Ethics Committee (protocol: 2015-322). Written informed consent was obtained from the families of all patients. Diagnosis, treatment and follow-up of the patients included in the study were realized between March 2003 and January 2015. A diagnosis of WD was made with presence of at least two of the following criteria: presence of KF ring, presence of familial history of WD, decreased ceruloplasmin level (<20 mg/dL), increased copper in 24-hour urine (>100 µg/24 h) and increased amount of copper in the liver (>250 µg/g dry tissue). Data related with familial history, age, age at the time of diagnosis, age at the time of occurence of neurological findings, follow-up time, gender, clinical and neurological examination characteristics, laboratory test results at the time of diagnosis, liver biopsy and brain magnetic resonance imaging (MRI) were obtained in all patients. Opthalmologic examination and familial screening were performed in the patients. D-penicillamine (initial dose 10 mg/kg/day, maintenance dose 20 mg/kg/day, maximum dose 1 000-1 500 mg/day) and zinc (75 mg/day) treatment was given to all patients. In the patients whose neurological findings did not resolve despite this treatment, D-penicillamine was discontinued and triethylentetramine (20 mg/kg/day) treatment was started. The patients were monitored in terms of the efficiency of the treatments given, potential side effects related with treatment and the clinical course of the neurological findings. During the follow-up period, biochemical tests including 24-hour urinary copper and serum free copper and detailed neurological examinations were performed. The prognosis of the patients were determined according to the course of the neurological findings. The prognosis was considered good in presence of improvement in neurological findings, moderate in absence of improvement in neurological findigns and poor in presence of progressive worsening in neurological findings after WD treatment.

Statistical analysis

All descriptive statistical analyses were performed using Statistical Package for the Social Sciences 22,0 (SPSS Inc.; Chicago, IL, USA) package program. The continuous variables were expressed as mean±standard deviation.

Results

Seven (58%) of the patients included in the study were female and five (42%) were male. The mean age at the time of diagnosis was 9.9±3.4 years (5-15 years) and the mean follow-up time was 49.0±36.4 months (15-128 months). The mean age at the time of occurence of neurological findings was 12.7±2.6 years (9-16 years). Seven (58%) of the patients presented with headace, seven (58%) presented with tremor, three (25%) presented with dystonia, two (17%) presented with ataxia, two (17%) presented with dizziness, one (8%) presented with acute weakness accompanied with numbness in the hands and one (8%) presented with syncope. Six patients (50%) had a positive familial history. A diagnosis of WD was made in three of these patients as a result of family secreening. The time between the diagnosis of WD and occurence of neurological findigns was 42.2±30.6 months (12-108 months) in nine patients (75%) who developed neurological findings during the follow-up period. Three patients (25%) presented with neurological symptoms and were diagnosed with WD as a result of systemic investigation. Laboratory tests revealed increased urinary copper in all patients (100%), hepatic dysfunction in 11 patients (92%), increased bilirubin in four patients (33%), anemia in four patients (33%), decreased albumin in three patients (25%) and abnormal coagulation tests in one patient (8%). The serum albumin level was decreased in 10 (84%) patients and normal in two patients (16%). The mean serum ceruloplasmin level was found to be 11.2±6.6 mg/dL (4-25 mg/dL). The mean urinary copper was found to be 181.6±65.1 mcg/24 h (108-315 mcg/24 h).

While dry copper weight was found to be increased in seven (78%) of nine patients who underwent liver biopsy, it was found to be normal in two patients (22%). The mean hepatic copper was found to be 274.9±62.7 µg/g dry tissue (156-350 µg/g dry tissue). On opthalmologic examination, KF ring was found in both eyes in six (50%) patients. Sunflower cataract was not found in any of the patients.

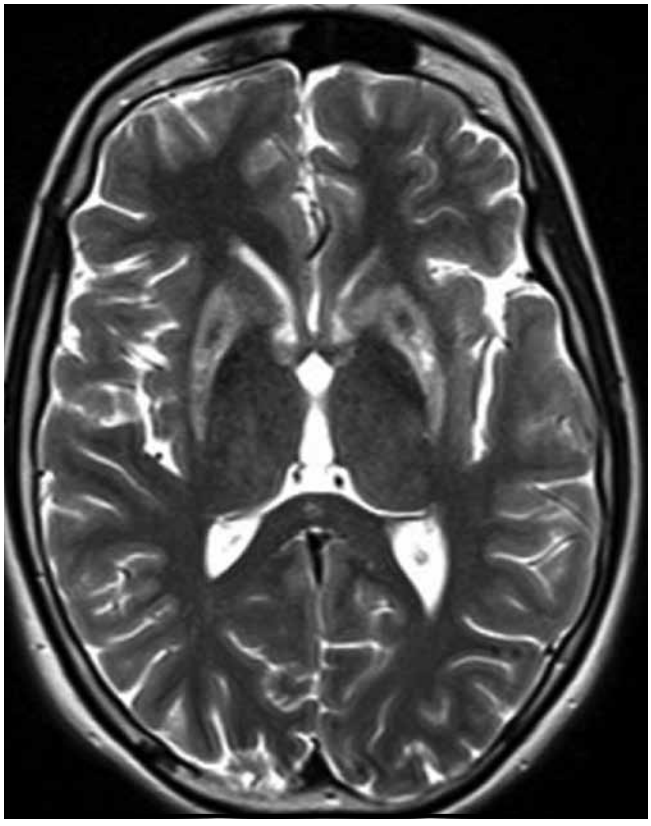

Figure 1. Hyperintense signal changes showing copper accumulation in the basal ganglia in our patient who developed progressive worsening in dystonia

Brain MRI was found to be normal in seven patients. Hyperintense nonspecific signal changes were observed in the subcortical white matter in the T2A flair sections in one patient on MRI. While hyperintense signal change was found in bilateral globus pallidus on T1-weighted images in two patients, hyperintense signal changes were found in the basal ganglia on T2-weighted images in one patient (Figure 1). Although tissue signals were found to be normal on MRI in one patient, the cerebellar tonsils were herniated 6.0 mm into the foramen magnum (accidental Chiari type 1). Improvement was found in both MRI and the clinical picture in one of our patients who had tremor during the follow-up period after treatment and who showed hyperintense signal change on T1-weighted images.

Six of our patients did not use their medications regularly before occurence of neurological findings. After the neurological findings occured, headache, dizziness, syncope and acute weakness accompanied with numbness in the hands improved completely with regular treatment in the first six months. A reduction in tremor was found in four of seven patients who had tremor and the clinical course did not change in three patients. Dystonia did not resolve in two of three patients who were found to have dystonia. Trihexyphenydile and L-dopa were added to the drugs used in one patient who was found to have progressive worsening in dystonia. The patient who did not benefit from these drugs became unable to walk without support because of dystonic posture. Tremor was also present in one of two patients who had ataxia and partial improvement was found in ataxia after treatment in this patient. Conclusively, the prognosis was good in terms of neurological findings except for movement disorders. In patients with movement disorder, the disease prognosis varied as good, moderate and poor. The clinical and laboratory features of the patients are summarized in Table 1.

Discussion

Although WD is most frequently manifested with hepatic and neurological features related with chronic accumulation of copper, it has a wide clinical spectrum (2-4, 6). The age of onset of neurological symptoms is frequently older compared to the age of onset of hepatic involvement. Although the diagnosis of WD is made in the first decade of life in children, the neurological symptoms of WD are mostly observed in the second decade (7, 8). In this study, the mean age at the time of diagnosis in our patients was 9.9 years and the mean age at the time of onset of neurological findings was 12.7 years which were compatible with the previous studies.

Although patients generally present with clinical findings related with hepatic dysfunction, patients without a diagnosis of WD who had presented only with neurological findings have been reported (7). In this study, three (25%) of our patients presented to our clinic with neurological findings and were diagnosed with WD as a result of systemic investigations.

Association of headache with WD has been reported, but it is still not clear if there is a relation between these two conditions (9). Headache was present in 58.3% of the patients in this study and only one patient had no previous diagnosis of WD (Table 1). This patient presented with headache and numbness and weakness in the hands and a diagnosis of WD was made when KF ring was found on opthalmologic examination. Wilson's disease should be considered in the differential diagnosis in patients with headache and unexplained neurological findings, though it is observed rarely and a complete ophtalmologic examination should be performed in these patient. Headache completely resolved after regular treatment in all our patients. This result supports that there is a relation between headache and

Table 1. Clinical and laboratory features in patients with Wilson's disease who had neurological findings

Subject number	Age at the time of diagnosis/Age at the time of occurrence of neurological findings/Age/Gender	Clinical findings at the time of diagnosis of WD	Laboratory findings at the time of diagnosis of WD	Neurological findings	Treatment	Prognosis
1	11 years/14 years/ 15 years/K	Paleness, jaundice, vomiting, Kayser-Fleischer ring	LFT ↑, Ceruloplasmin normal, Albumin ↓, Hb ↓, Bil ↑, urinary copper (+)	Tremor, Headache	D-penicillamine, Zinc	Moderate[2]
2[a]	15 years/16 years/ 16 years/E	-	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper normal	Tremor	D-penicillamine, Zinc	Good[1]
3	12 years/14,5 years/ years/E	Paleness, jaundice, vomiting, Kayser-Fleischer ring, Fulminant hepatitis	LFT ↑↑, Bil ↑, Albumin ↓, Hb ↓, Ceruloplasmin ↓, urinary copper (+), PT ↑, aPTT ↑	Tremor	D-penicillamine, Zinc	Good[1]
4	7 years/16 years/ 17 years/K	Paleness, jaundice, kusma, vomiting, Kayser-Fleischer ring, Fulminant hepatitis	LFT ↑↑, Bil ↑, Albumin ↓, Hb ↓, Ceruloplasmin ↓, urinary copper (+)	Dystonia, Tremor, Headache	Triethylenetetramine, Zinc	Moderate[2]
5[b]	15 years/15 years/ 15 years/K	Kayser-Fleischer ring	LFT ↑, Ceruloplasmin normal, urinary copper (+), Hepatic dry copper normal	Ataxia Tremor	D-penicillamine, Zinc	Good[1]
6[b]	13 years/13 years/ 14 years/E	Kayser-Fleischer ring	Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Ataxia, Dystonia, Tremor	Triethylenetetramine, Zinc, L-dopa, trihexyfenidyl	Poor[3]
7	10 years/11,5 years/ 13 years/K	Vomiting	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Tremor, Headache	D-penicillamine, Zinc	Good[1]
8	7 years/9 years/9 years/E	Vomiting, jaundice	LFT ↑, Bil ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Dystonia	D-penicillamine, Zinc	Moderate[2]
9[b]	10 years/10 years/ 11 years/E	Kayser-Fleischer ring	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Headache, Numbness and weakness in the hands	D-penicillamine, Zinc	Good[1]
10[a]	8 years/14 years/ 15 years/K	-	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Headache, Syncope, Dizziness	D-penicillamine, Zinc	Good[1]
11	6 years/9 years/ 13 years/K	Vomiting, jaundice, paleness	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Headache, diziiness	D-penicillamine, Zinc	Good[1]
12[a]	5 years/10 years/ 12 years/K	-	LFT ↑, Ceruloplasmin ↓, urinary copper (+), Hepatic dry copper ↑	Headache	D-penicillamine, Zinc	Good[1]

Bil: total bilirubin; Hb: Hemoglobin; LFT: Liver function tests; WD: Wilson's disease

[a]The patients number 2, 10 and 12 were diagnosed by way of familial screening.

[b]The patients number 5, 6 and 9 presented only with neurological findings at the time of the diagnosis of WD.

[1]The prognosis was considered good in presence of improvement in neurological findings in the follow-up period after WD treatment.

[2]The prognosis was considered moderate in absence of improvement in neurological findings in the follow-up period after WD treatment.

[3]The prognosis was considered poor in presence of progressive worsening in neurological findings in the follow-up period after WD treatment.

WD. The fact that headache responded to chelation treatment in all patients suggested that it might be related with the harmful effects of copper. Studies with large series should be conducted in this area.

The most commonly affected structures in the brain in patients with WD include the putamen, globus pallidus, nucleus caudatus, thalamus and brainstem (6). The neurological findings of WD are usually manifest-

ed with movement disorders in accordance with brain involvement. One of the most common neurological findings in WD is tremor. Tremor may be observed also during resting. However, it increases with movement and excitement. The severity of tremor may increase with progression of the disease (2-4, 9). The most common movement disorder observed in the patients in this study was tremor (it was found in seven (58%) of the patients). Therefore, WD should be considered in all patients who present with tremor. Improvement was observed in tremor in four patients in the first year of treatment (it occured only when the patients got excited). No improvement was found in tremor in the other three patients despite treatment.

Focal, segmental or diffuse dystonia may be observed in the face, pharynx, trunk and extremities in patients with WD. In some patient, "risus sardonicus" which is a continuous expression of smiling related with dystonia in the facial muscles may be observed. Severe contractions may occur in some other patients (2-4, 9-11). In our study, the clinical picture of dystonia did not improve in two of the patients and progressive worsening was found in dystonia in one patient. These findings suggest that treatment response and clinical prognosis are very variable in patients with WD who present with dystonia.

Ataxia related with involvement of the cerebellar system may be observed in patients with WD (2, 4, 10). In this study, ataxia was present in two (16.7%) of the patients. Tremor was also present in one of these two patients and improvement in ataxia was found after treatment in this patient. Dystonia and ataxia were present in the other patient. No improvement in the clinical picture of ataxia was observed in this patient. This shows that ataxia mostly accompanies other movement disorders.

Kayser-Fleischer ring is a significant finding of WD, but it is not a specific sign and may also be observed in other hepatic diseases including biliary cirrhosis, though rarely. Kayser-Fleischer ring is observed less frequently in children compared to adult patients (2, 4). This ring is observed more frequently in patients with neurological findings compared to patients with hepatic findings (2, 4, 10). Development of this ring is primarily related with the time passed from the onset of accumulation of copper in tissues. Observation of KF ring more frequently in patients with neurological findings may be related with the fact that neurological findings emerge at more advanced ages. In previous studies, the frequency of KF ring in children with WD was reported to range between 38% and 76% (7, 12). KF ring was found in 50% of the patients included in this study. In contrast to the above-mentioned studies, our study included only children with neurological WD. Studies with larger series should be performed to determine the frequency of KF ring in patients with WD with neurological findings.

Brain MRI findings may be normal or show abnormal signal changes in patients with WD with neurological findings. In a study conducted with children, neurological findings were found in 40.7% of the patients with WD who had abnormal brain MRI findings (8). Abnormal MRI findings in WD include hyperintense signal changes in T1 and T2-weighted images in the basal ganglia. These signal changes may be related with edema, gliosis, loss of myelinization, necrosis of the nerve cells or cystic degeneration as a result of the harmful effects of copper on the brain tissues (8). Brain MRI findings may resolve after treatment in the follow-up period in some patients. In this study, hyperintense signal changes were found on T1 or T2-weighted images on brain MRI in only three patients. Improvement in MRI findings was found in one of these patients during the follow-up period after treatment which was compatible with the clinical state.

D-penicillamine, zinc, triethylenetetramine and amonnium tetratiomolibdate are used in treatment of WD. D-penicillamine is substantially efficient because it causes to a negative copper balance by increasing urinary copper excretion (2-4, 9-11). However, it may worsen the neurological picture in initial treatment in patients with neurological involvement (2, 4, 9-11). Zinc has been shown to decrease the level of metallothionein in the small intestines and to be substantially efficient in treatment of WD by preventing copper from entering into the circulatory system (2, 4, 9-11). Triethylenetetramine is a chelator which increases the urinary ecxretion of copper, but has less side effects compared to D-penicillamine (9-11). D-penicillamine and zinc treatment was given to all subjects in this study. One should ensure that treatment is used appropriately in patients who develop neurological findings under treatment. Treatment incompliance may lead to sudden neurological disorders. In six patients in this study, treatment compliance decreased during the period before neurological findings emerged.

Autonomic dysfunction is common in cases of WD. In a previous study, it was reported that dystonia, tremor and bradykinesia developed in the second month of the follow-up in a patient who had recurrent syncope and the patient was diagnosed with WD in the end (13). In our study, a diagnosis of WD was made in our patient who had the complaints of headache, dizziness and syncope and whose sibling had been diagnosed with WD. After WD treatment the patient's complaints resolved complet-

ley and did not recur throughout the follow-up period. Further studies are needed to elucidate the possible relation between autonomic dysfunction and WD.

In previous studies, rhabdomyolysis related with copper toxicity and hypokalemic muscle weakness were reported in WD patients with muscle weakness (14, 15). In our study, one patient presented to our clinic with numbness in the hands and muscle weakness and was diagnosed with WD. The laboratory findings of the patient revealed normal creatine kinase and potassium values and clinical symptoms resolved in the third month of treatment. Although this study could not explain the reason of these symptoms in cases of WD, it showed that this kind of symptoms might be present in the absence of rhabdomyolysis and hypokalemic muscle weakness. Further stuides are needed to investigate the etiopathogenetic mechanisms.

In recent years, the mechanisms of phenotypical differences in WD have attracted much interest and have been an important subject of study. The etiopathogenesis of this phenotypical variance is multifactorial and is largely related with different genetic, metabolic and nutritional features. The amount of copper in the diet and lipid and cholesterol metabolism may affect the prognosis of the disease to a great extent. The close relation between the copper and cholesterol metabolism pathways and frequent hepatosteatosis in patients with WD have led to the assumption that increased copper level may disrupt cholesterol metabolism in the brain and this may be involved in the clinical course of the neurological disorders related with WD (16). More than 500 mutations of the ATP7B gene have been reported (2, 4, 17). This variability in the ATP7B mutations may have different effects on the severity of neurological findings, prognosis and treatment response (17). We think that varying severity of clinical course of the neurological findings and different treatment responses in the patients included in this study are related with multifactorial etiopathogenetic causes.

Conclusively, detailed neurological evaluation should be performed in the follow-up of all children with WD. Wilson' disease should be considered in the differential diagnosis in patients who present with movement disorders, headache or unexplained neurological findings. Close monitoring is important because of variable severity of the clinical course, possibility of treatment incompliance and variable treatment response.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from all patients' parents or legal guardians of the children included.

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