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ORIGINAL ARTICLE

Neurological features and outcomes of Wilson's disease: a single-center experience

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Abstract

Wilson's disease (WD) is an autosomal recessive genetic disorder of copper metabolism, and WD patients can present with neurologic symptoms. We aimed to report the general characteristics and prognosis of a Turkish series of WD patients with neurological manifestations. A total of 12,352 patients were screened from the patient database, and 53 WD patients were included. Patients were classified based on the predominant neurological syndrome type including tremor, dystonia, parkinsonism, or discrete neurological signs and were classified as having "good outcome," "stable," and "poor outcome" according to their treatment response. There were 32 male and 21 female patients, aged 20–66 years. The mean follow-up was 11.3 ± 4.56 years. Sixty-two percent of patients presented predominantly with neurological symptoms. Neurological WD diagnosis was established after a mean time delay of 2.3 years from the WD diagnosis. The most common neurological manifestation was dystonia, followed by tremor and parkinsonism. Fifteen patients had a family history of WD. Consanguinity was present in 20 patients. Patients were treated with D-penicillamine, trientine, zinc salts, or their combinations. Besides the main treatments, 41 patients were on symptomatic treatment for neurologic symptoms. Thirty-six patients had a "good outcome," five patients were stable, and six patients had "poor outcome." Post-chelation neurological worsening was observed in 11 patients. WD should be considered in differential diagnosis in any patient with unexplained neurologic symptoms. Early diagnosis is important, and appropriate treatment should be promptly initiated to prevent progressive and irreversible damage, with good prognosis and stable disease in the majority of the patients with treatment compliance.

Keywords Neurologic · Outcome · Prognosis · Wilson's disease

Introduction

Wilson's disease (WD) is an autosomal recessive genetic disorder of copper metabolism and is caused by an ATP7B gene mutation. Defective ATP7B gene function impairs both copper incorporation into ceruloplasmin in hepatocytes and copper release into bile, resulting in copper accumulation in various organs, such as the liver, cornea, brain, and kidneys [1].

Wilson's disease begins with a presymptomatic period during which copper accumulates in the liver. Up to 60% of patients present with hepatic symptoms at diagnosis, and up to 100% have at least subclinical laboratory signs of liver damage throughout the disease. Between early childhood and the fifth or sixth decade of life, but with a peak incidence of around 17 years, patients present with neurologic (tremor, dystonia, parkinsonism, dysarthria, dysphagia, dysexecutive syndrome, etc.); psychiatric (depression, psychosis, etc.); ophthalmologic (Kayser–Fleischer (KF) ring and sunflower cataract); and occasionally endocrinologic, cardiologic, and/or skeletal symptoms [2–5].

Wilson's disease is one of the few metabolic disorders that can be successfully treated by specific and effective pharmacological agents with good compliance (especially during presymptomatic period), so early diagnosis and treatment help to prevent irreversible damage in the majority of cases.

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There are few published studies on the prognosis of patients with WD with neurological manifestations in the literature, and a large series on this subject has not been published in our country before. This study aimed to report the general characteristics and prognosis of a Turkish series of WD patients with neurological manifestations.

Materials and methods

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was waived by the Local Ethics Committee in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

Besides clinical history and physical examination, the diagnosis of WD was based on a combination of tests proposed by the Working Party at the 8th International Meeting on Wilson's disease, Leipzig 2001 that reflects disturbed copper metabolism including low serum copper and ceruloplasmin, increased 24-h urinary excretion of copper, liver enzymes, slit-lamp examination to detect KF rings, and liver biopsy, when needed. All patients met 2012 Wilson's disease guideline's criteria of European Association for the Study of the Liver [1, 6].

Patients were classified based on the predominant neurological syndrome type at diagnosis by experienced neurologists using best clinical judgment and based on classifications described by Marsden [6] and Oder et al. [7], including tremor (predominant tremor), dystonia (choreoathetosis), parkinsonism (rigidity, rest tremor, and hypokinesia), or discrete neurological signs not covered by these classifications (such as slight dysarthria, dysphagia, drooling, epilepsy, neuropathy, gait abnormalities, tics, myoclonus).

Laboratory tests (complete blood cell count, biochemistry, urine analysis, serum copper, ceruloplasmin, 24-h urinary excretion of copper) were performed in the hospital laboratory using standard methods.

The patients were classified as having "good outcome," "stable," and "poor outcome" according to their response to treatment. Better neurological examination findings on the follow-up were defined as "good outcome," while stable or worse neurological examination findings were defined as "stable" and "poor outcome," respectively.

Statistical analysis

The demographic and clinical characteristics of the cohort were examined with independent samples *t* test for continuous variables and the chi-square test for categorical variables. Categorical variables were presented as numbers and percentages. Continuous variables were presented as mean and standard deviation (SD). Data were statistically analyzed with the SPSS software package. A p value of less than 0.05 was regarded as statistically significant.

Results

A total of 53 Turkish WD patients (32 male, 21 female), aged 20–66 years (38.6 ± 8.72 years), were included in the study. Six patients had one follow-up visit after the initiation of the treatment, while the others had follow-up visits. The mean follow-up was 11.3 ± 4.56 years (range: 1 month to 19 years). Twenty patients (38%) presented with predominantly hepatic symptoms, and 33 patients (62%) presented with predominantly neurological symptoms. The mean age of WD diagnosis was 20.6 ± 8.90 years, and patients presenting with neurological symptoms as the initial symptoms had a delayed age of diagnosis (21.1 vs. 19.9 years, $p = 0.650$). Neurological WD diagnosis was established after a mean time delay of 2.3 years from the WD diagnosis. Regarding all patients, 39.6% of patients were diagnosed before the age of 18 years. The most common neurological manifestation was dystonia (30.2%), followed by tremor (28.3%) and parkinsonism (9.4%). A large proportion of patients (32.1%) had other neurological manifestations, including dysarthria in eleven patients, dysphagia in three patients, myoclonus in one patient, ataxia in one patient, and seizure in one patient. Besides neurological symptoms, psychiatric symptoms (depression, anxiety disorder, catatonia, and psychosis) were observed in 17 patients (32.1%). The clinical features of the patients are summarized in Table 1.

Of the patients studied, 15 (28%) had a positive family history of WD, and consanguinity was present in 20 patients (38%). Our study cohort included two patients who were siblings, and the remaining patients did not have an affected sibling. Twenty-four-hour urinary copper excretion was raised in all patients. Four patients underwent hepatic biopsy, and all of them had a liver copper content ≥ 250 μg/g dry weight (422.3 ± 59.92 μg/g, range: 350–485 μg/g). All patients underwent ophthalmological examination, and KF rings were detected in 36% of patients on admission. However, the difference between patients with neurological symptoms and hepatic symptoms as the initial presentation was not significant in terms of KF rings ($p = 0.228$). MRI of the brain was performed in all patients, and all patients had abnormal MRI with increased signal intensity, mostly in putamen, talamus, and brainstem, on T2-weighted images, which was the most characteristic abnormality. Figure 1 shows these characteristic changes in one of our patients.

Patients were treated with D-penicillamine, trientine or zinc salts, or their combinations. Regarding current treatments, a total of 43 patients were on these medical treatments for WD.

Table 1 Characteristics and laboratory values of the study cohort

	n	Mean ± SD or %
Male gender	32	60%
Age (years)	53	38.6 ± 8.72
Age at WD diagnosis (years)	53	20.6 ± 8.90
Disease duration (years)	53	18 ± 7.91
WD to neurologic involvement (years)	53	2.3 ± 4.85
Neurologic involvement duration (years)	53	15.7 ± 8.13
Neurological involvement as the initial presentation	33	62%
Predominant neurological manifestation		
Tremor	15	28.3%
Dystonia	16	30.2%
Parkinsonism	5	9.4%
Other	17	32.1%
Dysarthria	11	20.7%
Dysphagia	3	5.7%
Ataxia	1	1.9%
Myoclonus	1	1.9%
Seizure	1	1.9%
Psychiatric symptoms	17	32.1%
Parental consanguinity	20	38%
Positive family history of WD	15	28%
Liver biopsy	4	7.6%
Liver copper content (μg/g)	4	422.3 ± 59.92
Presence of Kayser-Fleischer ring	19	36%
Abnormal brain MRI	53	100%
Treatment		
D-penicillamine	18	34%
Trientine	20	38%
Zinc salts	32	60%
Symptomatic drugs	41	77%

WD Wilson's disease

Four patients (7.5%) were on D-penicillamine therapy, six patients (11.3%) on trientine, six patients (11.3%) on only zinc salts, 13 patients (24.5%) on a combination of D-penicillamine and zinc salts, 13 patients (24.5%) on a combination of trientine and zinc salts, and one patient (1.9%) on a combination of D-penicillamine and trientine. One patient underwent liver transplantation due to liver failure. Besides anti-copper treatments, 41 patients were on symptomatic treatment for WD-associated neurologic symptoms. These treatments included (a) beta-blockers in 14 patients and botulinum toxin in one patient for tremor; (b) botulinum toxin in 6 patients, anticholinergic in 14 patients, and baclofen in 6 patients for dystonia; and (c) levodopa in 5 patients for parkinsonism. Three patients were non-adherent to treatment, and six patients did not attend follow-up examinations. None of the patients became symptom-free during follow-up. Thirty-six patients had a "good outcome," as they had better neurological examination findings on the follow-up, but they were left with some minor neurological deficit. Five patients were stable, while six patients had "poor outcome." The remaining six patients were not included as they only had one follow-up visit after the initiation of the treatment.

Neurological worsening following chelating treatment was observed in 11 patients (D-penicillamine in 8 patients and trientine in 3 patients). The neurological worsening was temporary in three patients; however, four patients remained as having poor outcome, and the remaining four patients were lost to follow-up.

Discussion

Prognoses of WD patients with neurological manifestations are limited because the number of patients available to compose a relevant study is frequently low. Although reports from

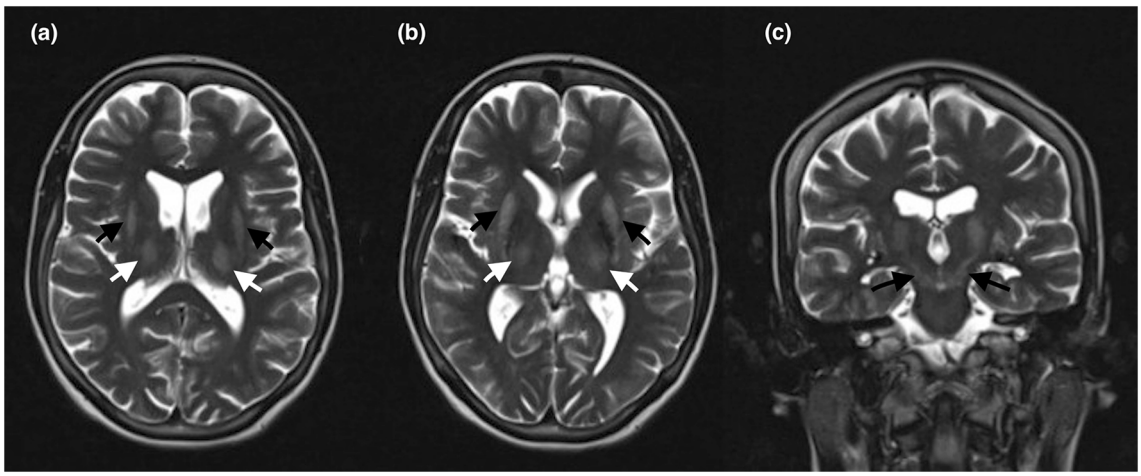

Fig. 1 Characteristic magnetic resonance imaging (MRI) abnormalities in one of the patients. Bilateral hyperintensity involving putamen (black arrows) and thalamus (white arrows) on axial MRI sequences (**a**, **b**) and brainstem hyperintensity (black arrows) on coronal MRI sequences (**c**) in T2-weighted images are shown

other countries and pediatric case series from Turkey were published before [8], this is the first study on a large Turkish series of WD patients with neurological manifestations.

Like other rare autosomal-recessive diseases, WD is present at a low frequency in all populations with an estimated frequency of 1 in 30,000; however, this may increase particularly in case of consanguineous marriages [9, 10]. According to the Turkey Demographic and Health Survey, the consanguineous marriage frequency in Turkey has varied between 22.0 and 29.2% from 1968 to 2008 and has increased over the years [11]. In the present study, parental consanguinity was 38%, with a possible founder effect on our cohort. In the absence of consanguinity, the chances of WD occurring are related to the population carrier frequency. Given the carrier frequency of 1/90 and diverse phenotype of WD, familial screening should be performed in first-degree relatives of the patients with WD [1, 12]. Wilson's disease occurs in siblings (25%) and the offspring (0.5%) [13], but the risk also exists for the previous generation (0.5%), although rare [14]. In our study, the WD family history was positive in 15 patients (28%). Family screening was found to be useful in diagnosing patients with WD at an early and most often asymptomatic or presymptomatic stage of disease [15].

Although the patient is presymptomatic during copper accumulation in early life, WD may become symptomatic at any age and should be considered in any patient presenting with unclear hepatic or neurologic disease. The peak incidence is around 17 years [16], with hepatic symptoms presenting around 11.4 years of age and neurological symptoms around 18.9 years of age [17]. Similar to the literature, 39.6% of patients were diagnosed before the age of 18 years in our study. In theory, thinking of the diagnosis of WD is usually straightforward in a child with liver manifestation or an adolescent with changes in personality and disturbances of movement, when associated with the laboratory findings. However, data from different WD cohorts show that diagnosing this rare disease remains challenging as the mean time between the first symptoms and the diagnosis usually exceeds 2 years [15, 18]. In every WD cohorts, neurological presentation is associated with significantly longer time from onset of symptoms to diagnosis than in hepatic presentation, ranging from 2.5 to 6 years [19, 20]. In our study, there was a mean of 2.3 years between hepatic and neurological symptoms.

Neurological symptoms are the initial clinical manifestation of WD in 40 to 60% of individuals [21]. The most common neurologic symptom observed in WD is tremor, and it is the first clinical manifestation in up to 55% of WD patients with neurologic symptoms [2, 7]. In the neurologic presentation of WD, the tremor can be of any type, including resting, postural, or kinetic. In our cohort, the tremor was a common (28.3%) neurological symptom. Dystonia may be the most severe, disabling, and treatment-refractory neurologic presentation of WD and is reported as an initial symptom in 11–65% of patients [2]. Dystonia was observed in 30.2% of patients in our study cohort. Parkinsonism may be manifest in approximately 40% of patients with WD, and this rate was 9.4% in our cohort [22]. Some authors have hypothesized that psychiatric symptoms indicate a more severe or advanced disease, may signal irreversible brain damage, or are secondary to metabolic disturbances produced by liver disease [23]. Although MRI abnormality was present in all of our patients, the psychiatric symptoms were present only in 32% of the patients.

Slit-lamp examination by an experienced examiner is a part of the diagnostic evaluation for suspected WD since the classic ophthalmologic manifestations of WD include KF ring and sunflower cataract. Diagnostic vigilance is essential because KF rings may be absent in up to 50% of patients with WD [24]. The absence of KF rings does not exclude the diagnosis of WD, even in patients with predominant neurological disease [1]. Kayser–Fleischer rings were present in 36% of the patients in our study, and patients with KF rings had more neurological symptoms as the initial presentation (63%). Wilson's disease is characterized by the classic triad of low serum ceruloplasmin, low total copper, and increased 24-h urinary copper excretion. Although our mean values were consistent with the literature, four patients required liver biopsy for definitive diagnosis. Liver biopsy was performed in 4 patients, and in line with the literature, the mean measured liver copper content was elevated. Genetic testing is challenging, as over 350 different mutations have been identified in different exons, and most mutations found only in a single patient. A study by Papur et al. [25] screened mutations of the ATP7B gene in unrelated Turkish WD patients (n = 46) and identified 24 different WD-related mutations in 30 patients. Of these mutations, five were found to be novel. In another study, Papur et al. detected 15 different mutations in the ATP7B gene in 23 out of 32 pediatric patients [26].

A variety of treatment approaches have been utilized in the treatment of WD, and treatment options include the copper chelators (D-penicillamine, trientine, and tetrathiomolybdate) and/or zinc salts. A combination with a low-copper diet is recommended. The best therapeutic approach remains controversial, as no prospective clinical trials have compared the different treatments. The European guidelines recommend the chelators as first therapy in symptomatic patients [1], and 69.7% of patients in our study were on chelator treatment either in combination with zinc salts or alone. Due to the different mode of action, treatment with zinc salts is less often associated with paradoxical deterioration after initiation of therapy, but they have a lower treatment efficacy. In our cohort, only six patients were on zinc monotherapy during the follow-up, and it was used in combination with chelators in 49% of the patients. Liver transplantation is a rare consideration in WD since the disease is usually responsive to medical therapy. In our series, only one patient with hepatic failure

(2%) underwent liver transplantation in our cohort. Regarding our study cohort, none of the patients became symptom-free during follow-up. Thirty-six patients had a "good outcome," 5 patients were "stable," and 6 patients had a "poor outcome." The remaining six patients were not included as they only had one follow-up visit after the initiation of the treatment.

Among WD patients with neurological symptoms, neurological worsening sometimes accompanies the start of a chelating agent, especially D-penicillamine. The percentage of these patients previously has been published to range from 3 to 30% [1, 27–29]. In our study, neurological worsening was observed in 11 patients. Similar to the literature, D-penicillamine treatment was associated with more worsening (8 vs. 3 patients). As stated by Walshe and Yealland [28], this worsening was temporary in three patients; however, four patients remained as having poor outcome, and the remaining four patients were lost to follow-up.

In patients that have persistent disabling neurologic symptoms despite adequate treatment and in patients presenting with severe neurologic symptoms at diagnosis, such as tremor, dystonia, and parkinsonism, such patients may benefit from symptomatic treatment to alleviate neurologic symptoms. Although there are currently no guidelines, these treatment options include pharmacotherapy, neurosurgery, physiotherapy, and speech therapy [30]. Of our study cohort, 41 patients were on symptomatic treatment for WD-associated neurologic symptoms.

Conclusion

Wilson's disease is a rare genetic disorder that should be considered in the differential diagnosis in any patient with unexplained neurologic, psychiatric, or hepatic dysfunction, even though they may not conform to the stereotypic presentation of this disorder. The incidence of this autosomal-recessive disease is high due to increasing consanguineous marriage frequency in Turkey. Early diagnosis of WD is of utmost importance, and appropriate treatment should be promptly initiated and maintained in order to prevent progressive and irreversible damage, with good prognosis and stable disease in the majority of the patients with treatment compliance.

Data availability All data are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was waived by the Local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Informed consent Informed consent has been taken from all patients.

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