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Evaluation of neurologically symptomatic and asymptomatic patients in childhood Wilson's disease with central nervous system involvement: A retrospective observational study

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Abstract

Aim: The aim was to evaluate the clinical and laboratory characteristics of children with Wilson's disease (WD) with and without neurological presentation with abnormalities on brain magnetic resonance imaging (MRI) and to describe the relationship of these observations with disease severity and functional outcome and their impact on prognosis.

Materials and Methods: Demographic, neuropsychiatric findings, laboratory, disease severity and functional results of 48 children with neurologically symptomatic and asymptomatic WD were evaluated retrospectively.

Results: A significant positive correlation was found between the neurologic symptom score and functional outcome in WD with neurological presentation ($p<0.001$). A significant positive correlation was found between disease severity scores (PELD, MELD, Child Pugh and Dhwin score) and modified Rankin scores (mRS) in WD without neurological presentation ($p<0.001$, 0.004, <0.001, 0.001, respectively). In addition, a significant positive correlation was found between total bilirubin, direct bilirubin and International Normalized Ratio (INR) values and mRS scores ($p= 0.006$, 0.012, 0.004, respectively). Kayser-Fleischer Ring sign in the eye was higher in the group with neurological symtomatic WD ($p<0.001$). The number of patients presenting with clinic of fulminant hepatitis and hepatic encephalopathy was significantly higher in the neurological asymptomatic group ($p<0.001$).

Conclusion: Brain MRI changes may occur even in hepatic WD and presymptomatic cases, although infrequently, regardless of the presence of neurological symptoms. It should be known that neurological symptoms in children and adolescents may occur without significant liver disease. Even without neurological symptoms, all children with WD should have a brain MRI before treatment.

Introduction

Wilson's disease (WD) is an autosomal recessive copper metabolism disorder characterized by excessive copper accumulation mainly in the liver and brain as a result of copper transport defect caused by mutations in the ATP7B gene [1]. The prevalence of WD symptomatic disease ranges from 1 in 30.000-100.000, however, there may be a higher prevalence of genetic WD [2]. The clinical phenotype of WD is diverse. Children most often present with hepatic manifestations, but a mild neurological disease may already be present. WD tends to show neurological or psychiatric symptoms in older children, teenagers and adults (1). The mean age at diagnosis of clinical manifestations of WD in childhood is 13 years (range 3-40 years) [1,3]. Neurological WD can occur without obvious signs and symptoms of liver disease. Neurological symptoms at the first presentation in WD have been reported at a rate of approximately 18–68% [4]. The main motor symptoms identified in children with neurological WD are tremor, mild ataxia, drooling and dysarthria. Speech difficulty is the most common initial symptom. A rapidly progressive dystonia rarely occurs [3]. Less common neurological findings include bradykinesia, facial grimacing, dystonia, tremor, rigidity intentional tremors, urinary incontinence, hyperreflexia, and cognitive impairment [1]. Mood disorders associated with depression and anxiety are the main psychiatric symptoms in pediatric patients [3]. Symptoms of acute personality changes, aggression and irritability in children are mistaken for normal adolescent behavior or substance abuse. Symptoms of learning disabilities in

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children may not be very noticeable. Cognitive difficulties at school may be associated with reasons such as hospital visits and medication side effects [1].

Brain MRI is the most important neuroradiological examination for diagnosis and may be helpful for monitoring treatment. Abnormalities on WD brain MRI include symmetrical hyperintense changes observed on T2-weighted images in the basal ganglia (especially putamen and caudate nuclei), thalamus, midbrain and pons [5]. In advanced cases, these abnormalities may appear on T1-weighted images as hypointense changes reflecting severe tissue damage. The image defined as the face of the giant panda in the midbrain is the most prominent WD changes [6]. In advanced cases, there is diffuse brain atrophy that becomes evident in the subcortical region and upper brain stem. Especially in WD cases with cirrhosis and hepatic encephalopathy, an increase in signal can be observed on T1-weighted images in the globus pallidus as well as in the substantia nigra, possibly due to manganese accumulation [7]. Characteristic brain MRI changes occur in almost 100% of drug-naive neurological WD patients, 40-75% of patients with hepatic symptoms, and 20-30% of presymptomatic patients [5]. There is no clear relationship between lesion localization and symptoms, but it has been reported that changes in the thalamus and pons show negative results [5]. MRI should be performed in all patients before initiating treatment, as brain MRI changes are observed even in hepatic or presymptomatic cases, regardless of the presence of neurological symptoms.

The clinical course in WD is variable and it is difficult to predict the poor prognosis [1,3,8]. In this context, we planned to evaluate the clinical and laboratory features of a cohort of neurologically symptomatic and asymptomatic children with CNS involvement and describe their long-term outcomes. We aimed to investigate the relationship and prognostic significance of these observations with disease severity and functional outcome. Our study differs from other clinical studies in terms of comparing the disability score at the last follow-up with the clinical and laboratory characteristics and severity of the disease in children with WD who have brain MRI abnormalities, with and without neurological presentation.

Materials and Methods

In this study, a retrospective observational analysis of a cohort of children under the age of 18 who were followed up with a diagnosis of WD in the Pediatric Gastroenterology and Pediatric Neurology Units of Inonu University Faculty of Medicine between January 2000 and January 2023 was performed. Children with WD who had hyperintense signal changes on brain MRIs were included in the study. All were followed for at least one year. Patients with WD were grouped as neuropsychiatric symptomatic and asymptomatic. Patients with hepatic WD without abnormal findings on brain MRI, those who were referred to our center only for liver transplantation, not evaluated by a child neurologist, those without clinical follow-up for at least one year, patients with missing information in their medical records or who were out of follow-up were excluded from the study. Some of our patients who had liver transplantation (LT) in the follow-up were decided by a multidisciplinary team to list for LT according to the transplant guidelines. The primary output/endpoint variable(s) of this study are; The aim of this study was to investigate the relationship between neuroimaging, disease severity and functional outcome in children with WD with CNS involvement, according to the presence or absence of neurological symptoms. Complete count sampling was used because pediatric Wilson's disease is a disease with a low prevalence. The study, retrospectively using purposive sampling (nonprobablity sampling) method. Since the fundamental assumption of the power analysis was not fulfilled. It was prepared according to the STROBE guidelines recommended for observational original research studies, which are consistent with this study design. The study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (number: 2023/4542). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was not obtained from the participants due to the retrospective nature of the study.

All clinical, laboratory and radiological information was entered into the hospital database and recorded. Age at presentation, gender, family history of WD, consanguinity, neurological and psychiatric symptoms, Kayser-Fleischer (K-F) ring sign in the eye, neurological examination findings and movement disorders, age at the onset of neurological findings, follow-up periods, whether liver transplantation was performed, laboratory tests performed at admission (full blood count, AST, ALT, GGT, total bilirubin, albumin, INR, ceruloplasmin, urinary copper excretion levels, biochemical, metabolic tests), PELD (Pediatric End Stage Liver Disease Model), MELD (Model for End Stage Liver Disease), Child Pugh and Dhwin scoring systems showing WD-related disease severity and mortality estimation, neuroimaging findings were recorded. Neurological functional outcomes of the patients were evaluated with the Modified Rankin Scale (mRS) for children. Positive outcome mRS score ≤ 2; poor outcome was defined as >2 [9]. Neurological and psychiatric symptoms and neurological examination findings of the patients were filled according to a pre-prepared questionnaire template from detailed and regularly kept medical records. A scoring system developed to describe the development of patients' neurological and psychiatric symptoms was defined as suggested in other studies [10,11]. A 12-item neuropsychological scoring system (12-60 points, where 1 point for each item is none and 5 points severe) and a 19-item neuropsychological scoring system (0-19 points, here each item is 1 point). The items of the scores partially correspond to the items selected by the EuroWilson registry and partially to the items used in the Unified Wilson Disease Rating Scale for WD [11,12,13].

Statistical analysis

The variables used in the study were summarized with mean, standard deviation, median, minimum and maximum values, frequency and percentage according to measurement levels. The assumption of normal distribution for numerical variables was examined using the Shapiro-Wilk test. For quantitative variables, to examine significance

difference between groups, Mann-Whitney U test was performed. For qualitative variables, Yates' chi-square with continuity correction and Fisher's exact tests were used where appropriate. P≤0.05 was accepted as statistical significance level. IBM SPSS Statistics 27 program was used in the analysis.

Results

Patients pediatric with WD were neurologically classified into two groups as symptomatic and asymptomatic. There were 48.0% (23) children in the symptomatic group and 52% (25) in the asymptomatic group without neurological symptoms but with brain MRI changes. Patients with WD were underwent 11 LT from a living donor and 8 from a cadaver. Specific hyperintense signal changes were detected in the subcortical white matter and basal ganglia on T2W flair sections in the brain MRIs of the patients. In patients with neurological symptomatic WD, hyperintense signal changes were observed in the globus pallidus 14 (60.9%), thalamus 4 (17.4%), putamen 16 (69.6%), caudate 11 (47.8%) and brainstem 2 (8.7%). Hyperintense signal changes were detected in the bilateral globus pallidus on T1-weighted images in brain MRIs of patients without neurological presentation.

Comparison of patients neurologically symptomatic and asymptomatic with Wilson's disease

There was no significant difference between symptomatic and asymptomatic groups in terms of age and gender (p>0.05). Consanguinity and family history of WD were similar between the two groups (p>0.05). The clinical follow-up period was longer in children with WD with neurological presentation (p=0.01). The number of patients who underwent LT from a living donor was significantly higher in the neurological symptomatic WD group (p=0.04). K-F ring sign was statistically significantly higher in the WD group with neurological symptomatic WD (p<0.001). The number of patients presenting with the clinic of fulminant hepatitis and hepatic encephalopathy was significantly higher in children with neurological asymptomatic WD (p<0.001). In the neurological asymptomatic group, AST, ALT, GGT, Total bilirubin and INR levels were significantly higher than the children with neurological symptomatic WD (p= 0.003, 0.012, 0.016, <0.001, 0.002, respectively). Disease severity scores of PELD, MELD, Child Pugh and Dhwin scoring systems in WD were significantly higher than in the neurological symptomatic WD group (p=0.051, <0.001, 0.002, 0.001, respectively). The number of patients with poor functional outcome (poor outcome >2) was significantly higher in the neurological asymptomatic but liver dysfunction group (p=0.008) (Table 1, Table 2).

Demographic and clinical characteristics of patients with Wilson's disease with neurological presentation

Mean age at diagnosis of patients with neurological symptomatic WD was 10.74 ± 2.61 years (range: 6 – 16 years), mean follow-up period was 7.8 ± 5.83 (1-23 years), and 44.4% (12) were male consisted of 23 patients. In this group, 12 (52.2%) patients underwent LT (9 living donors, 3 cadaveric). The mean age of the patients at the time of LT was 15.54 ± 4.82 years (range: 7 – 26 years). In the period after LT, two patients showed partial recovery, four patients did not improve, four patients progressed, and two patients died. K-F ring was detected in 18 children in ophthalmologic examination. Age of onset of neurological symptoms was 13.43 ±3.57 years (range 6-18 years). Neurological symptoms were found rest tremor 19 (82.6%), postural tremor 5 (21.7%), bradykinesia 9(39.1%), akathisia 2 (8.7%), walking difficulty 18 (78.3%), dysarthria 20 (87.0%), dysphagia 10 (43.5%), salivation 17 (73.9%), seizures 6 (26.1%), writing impairment 19 (82.6%), headache 10 (43.5%), rigidity 9 (39.1%), hand numbness 7 (30.4%), dysmetria 10 (% 43.5), pyramidal symptoms 7 (30.4%), visual tract impairment 1(4.3%), urinary incontinence 1(4.3%), movement disorder 17 (73.9%). Among the movement disorders were recorded, dystonia 13 (76.5%), choreoathetosis 3 (17.6%), ataxia 8 (47.1%), myoclonus 5 (29.4%), akinetic rigid syndrome 1 (5.9%) and parkinsonism 1 (5.9%). Psychiatric symptoms were detected decrease in school success 17 (73.9%), depression 9 (39.1%), behavioral disorder 6 (26.1%), forgetfulness 12 (52.2%), fatigue/weakness 20 (87%), eating disorder/anorexia 5 (21.7%), psychosis 5 (21.7%), and insomnia 17.4% (4). The mean neurological score (Mean ±SD) of the patients was 35.21±14.01 (15-55 points) and the mean psychiatric score was 3.39±2.03 (1-8 points). The modified Rankin scores associated with functional outcome were 3.78 ± 1.44 (range 2 to 6) points and were classified as poor prognosis in 17 patients and good prognosis in 6 patients. A significant positive correlation was found between the patients' neurologic symptom total score and mRS scores (p <0.001) (Table 3). There was no significant correlation between the patients' neurologic symptom total score and laboratory parameters and disease severity scores (PELD, MELD Child-Pugh Score and Dhwin Scores) (p > 0.05). There was no significant correlation between functional outcome and laboratory results and disease severity scores (p > 0.05) (Table 3).

Demographic and clinical characteristics of patients with Wilson's disease without neurological presentation

The mean age at the time of diagnosis of 25 neurologically asymptomatic patients was 10.4 ± 3.76 years (range: 5 to 17 years) and 55.60% (15) were boys. The mean follow-up period of the patients was 3.84 ± 3.21 years (1 - 11) years. LT was administered to seven patients, the mean age at the time of transplantation was 12.86 ± 3.93 (7 - 18) years. The patients' mRS at admission were 4.36 ± 1.19 (3 - 6) points. A significant positive correlation was found between patients' mRS scores and total bilirubin, direct bilirubin and INR values (p= 0.006, 0.012, 0.004, respectively). In addition, a significant positive correlation was found between mRS scores and PELD, MELD, Child Pugh and Dhwin scores (p <0.001, 0.004, <0.001, 0.001, respectively) (Table 4).

Discussion

This study demonstrates that severe neurological impairment is associated with poor functional outcome in neurological symptomatic WD. It also shows that severe disease severity and therefore high total bilirubin, direct bilirubin

Table 1. Comparison of neurologically symptomatic and asymptomatic Wilson disease patients.

Variables*	Categories	Neurological sign			X^2 statistics	p
		No (n=25)	Yes (n=23)	Total		
Gender	Girl	10[a] (47.60%)	11[a] (52.40%)	21 (100.00%)	0.065	0.799[2]
	Boy	15[a] (55.60%)	12[a] (44.40%)	27 (100.00%)		
Consanguinity	No	4[a] (44.40%)	5[a] (55.60%)	9 (100.00%)	-	0.719[3]
	Yes	21[a] (53.80%)	18[a] (46.20%)	39 (100.00%)		
Family history	No	16[a] (59.30%)	11[a] (40.70%)	27 (100.00%)	0.701	0.402[2]
	Yes	9[a] (42.90%)	12[a] (57.10%)	21 (100.00%)		
Kayser-Fleischer ring	No	16[a] (76.20%)	5[b] (23.80%)	21 (100.00%)	7.061	**0.008[2]**
	Yes	9[a] (33.30%)	18[b] (66.70%)	27 (100.00%)		
Liver Transplantation	No	18[a] (62.10%)	11[a] (37.90%)	29 (100.00%)	6.572	**0.04[1]**
	Living donor	2[a] (18.20%)	9[b] (81.80%)	11 (100.00%)		
	Cadaveric	5[a] (62.50%)	3[a] (37.50%)	8 (100.00%)		
Liver Presentation	Chronic Hepatitis	11[a] (57.90%)	8[a] (42.10%)	19 (100.00%)	22.429	**<0.001[1]**
	FulminantHepatitis	14[a] (87.50%)	2[b] (12.50%)	16 (100.00%)		
	Neurowilson	0[a] (0.00%)	13[b] (100.00%)	13 (100.00%)		
Hepatic Encephalopathy	No	10[a] (30.30%)	23[b] (69.70%)	33 (100.00%)	20.073	**<0.001[1]**
	Stage 1	7[a] (100.00%)	0[b] (0.00%)	7 (100.00%)		
	Stage 2	8[a] (100.00%)	0[b] (0.00%)	8 (100.00%)		
Modified Rankin Scores	Good	0[a] (0.00%)	6[b] (100.00%)	6 (100.00%)	–	**0.008[3]**
	Bad	25[a] (59.50%)	17[b] (40.50%)	42 (100.00%)		
Total		25 (52,01%)	23 (47.99%)	48 (100.00%)		

*: Variables are expressed as frequency (percent) 1: Pearson chi-square, 2: Continuity correction, 3: Fisher's exact test Each subscript letter denotes a subset of GBS categories whose column proportions do not differ significantly from each other at the 0.05 level The statistically significant difference is expressed in bold.

Table 2. Comparison of neurologically symptomatic and asymptomatic Wilson disease patients.

Variables*	Neurological sign		p**
	No (n=25)	Yes (n=23)	
Calendar Age	20.72 ± 3.89 | 20 (15 - 30)	21.61 ± 5.17 | 23 (7 - 31)	0.254
Diagnosis Age	10.4 ± 3.76 | 10 (5 - 17)	10.74 ± 2.61 | 10 (6 - 16)	0.604
LT Age	12.86 ± 3.93 | 13 (7 - 18)	15.54 ± 4.82 | 15.75 (7 - 26)	0.287
Clinical Follow-up	3.84 ± 3.21 | 3 (1 - 11)	7.8 ± 5.83 | 6.5 (1 - 23)	**0.01**
mRS Scores	4.36 ± 1.19 | 5 (3 - 6)	3.78 ± 1.44 | 4 (2 - 6)	0.129
Albumin	2.88 ± 0.73 | 2.7 (1.9 - 4.4)	3.29 ± 0.88 | 3.7 (1.7 - 4.5)	0.094
AST	266.6 ± 332.51 | 173 (23 - 1307)	96.91 ± 87.43 | 73 (15 - 354)	**0.003**
ALT	206.8 ± 294.12 | 131 (13 - 1145)	78.09 ± 98.85 | 40 (13 - 427)	**0.012**
GGT	129.8 ± 89.84 | 97 (19 - 309)	95.83 ± 125.57 | 45 (12 - 557)	**0.016**
Total Biluribin	12.1 ± 16.07 | 6 (0.5 - 47.5)	2.63 ± 4.76 | 0.9 (0.2 - 22.9)	**<0.001**
Direct Biluribin	10.28 ± 13.12 | 4.2 (0.1 - 34)	1.32 ± 2.42 | 0.5 (0 - 11.39)	**0.001**
INR	4.27 ± 5.74 | 3 (0.9 - 23)	1.7 ± 0.79 | 1.4 (0.9 - 4)	**0.002**
PELD scores	21.95 ± 12.05 | 21 (7 - 48)	14.02 ± 8.09 | 13 (1 - 29)	0.051
MELD scores	24.08 ± 10.3 | 26 (6 - 43)	12.49 ± 6.92 | 10 (6 - 29)	**<0.001**
Child-Pugh	9.92 ± 2.78 | 10 (5 - 13)	7.17 ± 2.71 | 5 (5 - 13)	**0.002**
Dhwin scores	0.76 ± 0.44 | 1 (0 - 1)	0.26 ± 0.45 | 0 (0 - 1)	**0.001**
Ceruloplasmine	0.12 ± 0.1 | 0.09 (0.01 - 0.5)	0.08 ± 0.05 | 0.08 (0.01 - 0.19)	0.147
Copper excrection in urine	895.08 ± 880.24 | 611 (25 - 2534)	504.26 ± 342.74 | 405 (31 - 1250)	0.38

*: Variables are expressed as mean ± std. deviation | median (minimum-maximum). **: Mann-Whitney U test The statistically significant difference is expressed in bold.

and INR values are associated with poor functional outcome in neurological asymptomatic WD. Our findings give an idea about the prognosis of WD with central nervous system (CNS) involvement in childhood.

Table 3. The relationship between neurological symptom scores, psychiatric symptom scores and Modified Rankin Scores in neurological symptomatic Wilson disease.

Variables	Psychiatric symptom scores			Neurological symptom scores			Modified Rankin Scores		
	rho*	p	n	rho*	p	n	rho*	p	n
Psychiatric symptom scores	1		23	0.438	**0.037**	23	0.404	0.056	23
Neurological symptoms scores	0.438	**0.037**	23	1		23	0.958	**<0.001**	23
Modified Rankin Scores	0.404	0.056	23	0.958	**<0.001**	23	1		23

*: Spearman's rho correlation coefficient The statistically significant difference is expressed in bold.

Table 4. The relationship between Modified Rankin Scores and laboratory variables in neurologically asymptomatic Wilson disease.

Variables	Modified Rankin Scores		
	rho*	p	n
Albumin	-0.368	0.071	25
AST	0.241	0.246	25
ALT	0.013	0.953	25
GGT	0.354	0.082	25
Total Biluribin	0.531	**0.006**	25
Direct Biluribin	0.493	**0.012**	25
INR	0.557	**0.004**	25
PELD score	0.797	**<0.001**	20
MELD score	0.56	**0.004**	25
Child-Pugh score	0.663	**<0.001**	25
Dhwin skore	0.635	**0.001**	25
Ceruloplasmine	-0.18	0.388	25
Copper extraction in urine	0.193	0.355	25

*: Spearman's rho correlation coefficient The statistically significant difference is expressed in bold.

In previous studies, neurological features, frequency, diagnosis and management of WD in children were evaluated [4,5,14]. In recent studies, structural and functional changes related to the disease have been shown in brain and functional MRI studies of patients with and without neurological presentation [15]. In our pediatric cohort, which we evaluated retrospectively, we hypothesized that there is a relationship between neuropsychiatric symptoms and disease severity at first admission and functional outcome at final follow-up. To the best of our knowledge, there has been no other study evaluating the relationship between clinical and laboratory features, disease severity scores, neurologic impairment assessment, and disability modified Rankin Scale in order to predict the clinical course in WD patients with brain MRI changes in childhood.

Due to the wide heterogeneity in addition to the combined neurological symptoms that occur in the course of WD, clinical scales such as the Unified Wilson's Disease Rating Scale (UWDRS) or the Global Rating Scale for WD have been established to evaluate neurological deficits and functional impairment [7,13,16]. A detailed neurological assessment, together with its impact on patients' activities of daily living, are important criteria in diagnosis and follow-up. These systems generate scores that describe the severity of neurological symptoms and enable more effective patient care. Standardized neurological evaluation results developed due to the wide spectrum of WD and the fluctuation of neurological symptoms allow both individual and inter-individual comparison. However, none of the neurological evaluation systems include the evaluation of liver function tests and therefore cannot be used to differentiate hepatic encephalopathy from neuropsychiatric WD [17]. As with many other liver diseases in which cirrhosis may be present, MELD and Child-Pugh scores are commonly used to reflect the severity of liver disease [6.18]. It is also used as diagnostic and follow-up tools to assess treatment efficacy or failure and detect significant changes in hepatic function. MELD is used for prognostic purposes of mortality in patients with advanced liver disease, higher scores indicate increased mortality [6,18]. Increased MELD indicates that medical treatment may fail or be inconclusive in the face of severe acute liver failure, while MELD declines with successful treatment of liver disease. In our study, a significant correlation was found between the increase in neurological symptom total scores and the increase in disability mRS scores in Wilson patients with neurological presentation. However, the increase in neurological symptom scores was not associated with the MELD, Child-Pugh Scores, which classify the severity of liver disease. In addition, no correlation was found between the increase in the severity of liver disease and the functional outcome and prognosis. Our findings showed that high neurologic symptom scores in neurologically symptomatic WD can give an idea about poor functional outcome and prognosis. Adequate evaluation of neurological impairment in WD can predict neurological disability in patients during follow-up. Neurological evaluation scores also showed that they cannot be used to determine disease severity since they do not evaluate hepatic functions. Severe hepatic impairment (increased disease severity) in neurologically asymptomatic WD was found to be associated with high total bilirubin, direct bilirubin and INR values, as expected. In addition, it showed a significant association between severe disease and poor functional outcome. This may be explained by the higher number of patients presenting with hepatic encephalopathy findings in the neurological asymptomatic group. In addition, liver function tests and the mentioned laboratory values were also higher and predicted higher disease severity in this context.

Damage to the central nervous system is caused both by direct copper toxicity and indirectly by hepatic encephalopathy [19]. Brain MRI changes may occur even in hepatic

WD and presymptomatic cases, although they are not frequent regardless of the presence of neurological symptoms [6,9]. Symmetrical hyperintensity on T1-weighted MRI is defined as a characteristic finding in hepatic encephalopathy. It is found in the globus pallidus and putamen, and as the disease progresses, the hypothalamus and midbrain are affected. This condition is attributed to mild astrocytic edema and manganese deposits [19,20]. MRI changes may be present before neurological or hepatic signs are detected and some may reverse after treatment. Abnormal signals in the basal ganglia may be the effect of glial cell hyperplasia, edema and necrosis caused by copper deposits, which may disappear after appropriate copper removal therapy [6,9]. On MRI of neurologically symptomatic patients, it characteristically presents with symmetrical T2 hyperintensity or mixed intensity in the deep gray matter (putamen, globus pallidus, caudate, and thalamic nuclei), mesencephalic, and pons white matter. The midbrain, cerebellum, corticospinal tracts, cortex and subcortical area are also affected [21]. High-signal-intensity lesions in the basal ganglia on T1-weighted images usually reflect hepatic involvement of WD, ie changes secondary to chronic liver disease. High signal intensity lesions on T2-weighted images reflect cerebral involvement of WD [21,22]. In our study, hyperintense signal changes were detected in the bilateral globus pallidus on T1-weighted sections in brain MRIs of patients without neurological presentation. This supports the view that abnormal bilateral T1 signals are associated with hepatic dysfunction.

Limitations

The retrospective nature of the study and its single-center nature may be limitations of this study. The low sample size is due to the rarity of WD in the pediatric age group.

Conclusion

The diagnosis and treatment of neuropsychiatric symptoms in children with WD is delayed due to a combination of lack of awareness, variable symptoms during experience and presentation, and variable clinical course. It should be known that neurological disease in children and adolescents can occur without significant liver disease. Even with a good response to medical treatment, families should be consulted about the development and progression of neuropsychiatric symptoms. Even without neurological symptoms, all children with WD should have a brain MRI before treatment.

Ethical approval

The study was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (number: 2023/4542).

References

1. Kerkar N, Rana A. Wilson Disease in Children. Clin Liver Dis. 2022;26(3):473-488.
2. Gao J, Brackley S, Mann JP. The global prevalence of Wilson disease from next-generation sequencing data. Genet Med. 2019;21(5):1155-1163.
3. Fernando M, van Mourik I, Wassmer E, Kelly D. Wilson disease in children and adolescents. Arch Dis Child. 2020;105(5):499-505.
4. Machado A, Chien HF, Deguti MM, et al. Neurological manifestations in Wilson's disease: Report of 119 cases. Mov Disord. 2006;21(12):2192-2196.
5. Członkowska A, Litwin T, Dusek P, et al. Wilson disease. Nat Rev Dis Primers. 2018;4(1):21. Published 2018 Sep 6.
6. Członkowska A, Litwin T. Wilson disease - currently used anticopper therapy. Handb Clin Neurol. 2017;142:181-191.
7. Kozić D, Svetel M, Petrović B, Dragasević N, Semnic R, Kostić VS. MR imaging of the brain in patients with hepatic form of Wilson's disease. Eur J Neurol. 2003;10(5):587-592.
8. Jopowicz A, Tarnacka B. Neurological Wilson's Disease Signs-Hepatic Encephalopathy or Copper Toxicosis?. Diagnostics (Basel). 2023;13(5):893. Published 2023 Feb 27.
9. Poujois A, Sobesky R, Meissner WG, et al. Liver transplantation as a rescue therapy for severe neurologic forms of Wilson disease. Neurology. 2020;94(21):e2189-e2202.
10. Yagci MA, Tardu A, Karagul S, et al. Influence of Liver Transplantation on Neuropsychiatric Manifestations of Wilson Disease. Transplant Proc. 2015;47(5):1469-1473.
11. Weiss KH, Schäfer M, Gotthardt DN, et al. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease. Clin Transplant. 2013;27(6):914-922.
12. Członkowska A, Tarnacka B, Möller JC, et al. Unified Wilson's Disease Rating Scale - a proposal for the neurological scoring of Wilson's disease patients. Neurol Neurochir Pol. 2007;41(1):1-12.
13. Leinweber B, Möller JC, Scherag A, et al. Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) in German patients with treated Wilson's disease. Mov Disord. 2008;23(1):54-62.
14. Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci. 2010;1184:173-187.
15. Tinaz S, Arora J, Nalamada K, et al. Structural and functional brain changes in hepatic and neurological Wilson disease. Brain Imaging Behav. 2021;15(5):2269-2282.
16. European Association for Study of Liver. EASL Clinical Practice Guidelines: Wilson's disease. J Hepatol. 2012;56(3):671-685.
17. Leinweber B, Möller JC, Scherag A, et al. Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) in German patients with treated Wilson's disease. Mov Disord. 2008;23(1):54-62.
18. Kamath PS, Kim WR; Advanced Liver Disease Study Group. The model for end-stage liver disease (MELD). Hepatology. 2007;45(3):797-805.
19. Hermann W. Morphological and functional imaging in neurological and non-neurological Wilson's patients. Ann N Y Acad Sci. 2014;1315:24-29.
20. Weissenborn K, Bokemeyer M, Ahl B, et al. Functional imaging of the brain in patients with liver cirrhosis. Metab Brain Dis. 2004;19(3-4):269-280.
21. Zhong W, Huang Z, Tang X. A study of brain MRI characteristics and clinical features in 76 cases of Wilson's disease. J Clin Neurosci. 2019;59:167-174.
22. Yu XE, Gao S, Yang RM, Han YZ. MR Imaging of the Brain in Neurologic Wilson Disease. AJNR Am J Neuroradiol. 2019;40(1):178-183.