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CLINICAL PRESENTATIONS OF WILSON DISEASE AMONG POLISH CHILDREN

OBRAZ KLINICZNY CHOROBY WILSONA WŚRÓD POLSKIEJ POPULACJI DZIECI

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Abstract

Introduction: *Wilson disease (WD) may present from early childhood up to the eighth decade, presenting with variable hepatic and neuropsychiatric symptoms. Establishing the diagnosis is straightforward if the major clinical and laboratory features are present. However, clinical phenotypes are highly varied and early, proper diagnosis can be challenging.*

Aim: *The aim of our study was to analyze clinical presentations and diagnostic tests of Polish pediatric patients with WD.*

Methods: *We retrospectively analyzed medical history of 156 patients with confirmed diagnosis of WD treated at our Institute from 1996 till March 2016.*

Results: *The mean age at onset of symptoms was 10.15±4.23 years of age. Hepatic presentation was the most common one (94.23%) with either liver failure (16.03%) or more frequently increased transaminases (78.2%). In 90.26% cases ceruloplasmin serum concentration was ≤0,2 g/l, in 51.93% patients basal urinary copper excretion was >100 µg/24 h. Mutation analysis was performed in 155 (99.36%) cases. The most common mutation was p.H1069Q.*

Conclusions: *Wilson disease can present with only significantly increased transaminases activity and hepatomegaly or liver failure, but neurological symptoms are very rare in children. Diagnostic approach is challenging due to wide spectrum of clinical presentations in a high variable degree of severity. Genetic screening is supportive, ceruloplasmin and urinary copper excretion are valuable tests in the majority of patients but do not allow to exclude WD.*

Key words: Wilson's disease, early onset of disease, diagnosis, mutation

Streszczenie

Wstęp: *Choroba Wilsona (WD) może ujawnić się od wczesnego dzieciństwa do osiemdziesiątego roku życia z różnym nasileniem objawów wątrobowych i neuropsychiatrycznych. Postawienie diagnozy jest stosunkowo proste, jeśli występują typowe objawy kliniczne i laboratoryjne. Jednak obraz kliniczny WD jest zróżnicowany i wczesne postawienie prawidłowej diagnozy nie zawsze jest oczywiste.*

Cel: *Celem naszej pracy była analiza obrazu klinicznego WD i wyników badań diagnostycznych w polskiej populacji pediatrycznej.*

Metody: *Retrospektywna analiza dokumentacji medycznej 156 pacjentów z potwierdzonym rozpoznaniem choroby Wilsona, znajdujących się pod opieką Instytutu od 1996 do marca 2016.*

Wyniki: *Pierwsze objawy u pacjentów pojawiały się w wieku 10,15±4,23 roku. Najczęstsza była postać hepatologiczna choroby (94,23%), ujawniająca się głównie jako podwyższona aktywność aminotransferaz (78,2%), rzadziej jako niewydolność wątroby (16,03%). Stężenie ceruloplazminy ≤0,2 g/l obserwowano u 90,26%, dobowe wydalanie miedzi z moczem >100 µg/24h u 51,93% dzieci. Badanie molekularne zostało wykonane u 155 (99,36%) przypadków. Najczęstszą stwierdzaną mutacją była p.H1069Q.*

Wnioski: *Choroba Wilsona w populacji pediatrycznej może się objawiać wyłącznie jako podwyższona aktywność aminotransferaz i powiększenie wątroby lub też jako niewydolność wątroby, natomiast objawy neurologiczne są bardzo rzadkie u dzieci. W związku z szerokim spektrum objawów oraz różnym ich stopniem nasilenia diagnostyka jest trudna. Badanie molekularne jest pomocne w postawieniu rozpoznania. Poziom ceruloplazminy i dobowe wydzielanie miedzi z moczem są ważnymi badaniami u większości pacjentów, jednak nie pozwalają na wykluczenie choroby Wilsona.*

Słowa kluczowe: choroba Wilsona, wczesne rozpoznanie, mutacja

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INTRODUCTION

Wilson disease (WD) is an autosomal-recessive human copper storage disorder caused by mutations within the gene *ATP7B* located on chromosome 13 with a prevalence in most populations of one in 30 000 [1]. It may present at any age from infancy (with raised transaminases retivity, measured for some unrelated reason) up to the eighth decade, presenting with variable hepatic and neuropsychiatric features related to the accumulation of copper in the liver,the lenticular nuclei, and cornea (Kayser-Fleischer ring). Establishing the diagnosis of Wilson disease is straightforward if the major clinical and laboratory features are present [2]. However, symptoms at any age are frequently nonspecific. Diagnosis of WD is challenging but essential, because prompt treatment is needed to prevent progression of hepatic and neurologic damage.

The aim of our study was to analyze clinical presentations and diagnostic tests of one of the largest single-center cohort of pediatric cases with Wilson Disease.

MATERIAL AND METHODS

Since 1996 up to March 2016 we identified WD in our pediatric clinic in 156 children. Data about medical history, family medical history, clinical presentation, biochemical parameters (alanine transaminase (ALT), asparganine transaminase (AST), bilirubin), complete blood count (CBC), coagulation parameters, serum ceruloplasmin concentrations and 24 hours urinary copper excretion before diagnosis, were collected. In most cases (130) liver biopsy was performed and in 85 patients hepatic parenchymal copper concentration was measured. WD was diagnosed based on the Ferenci scoring system [3, 4] (table I), with confirmation by mutational analysis in most cases.

Data were collected from patient's medical history and analyzed retrospectively. The frequency of findings was presented in numbers and in percentage. The distribution of parameters was presented as mean, standard deviation (SD) values and range.

RESULTS

At our center 156 pediatric patients (85 (55.1%) female) with confirmed diagnosis of WD were treated during the period of 1996 through March, 2016. The mean age at onset of symptoms was 10.15±4.23 years of age (2-17.5). The mean age at diagnosis was 11.56±4.08 years (2.5-20.5) [mean±SD (min-max)]. The mean delay of diagnosis was 1.43 years. The diagnosis of WD was confirmed in 13 cases before the age of 5 years.

Clinical presentation

Hepatic presentation of WD was observed in 147 (94.23%) patients, 6 (3.85%) children had both hepatic and neurological presentation. In 5 (3.2%) patients psychiatric features were found. In two cases abdominal pain was the only symptom. Seven (4.49%) were asymptomatic siblings of patients with Wilson's disease, in those cases the diagnosis was established before the onset of any clinical or laboratory symptoms. Hepatic presentation in this study included hepatitis (defined as elevated transaminases) in 122 (78.2%) cases, liver failure (acute or exacerbation of chronic) in 25 (16.03%) patients. In 5 children in course of liver failure encephalopathy had occurred. Neurological and psychiatric abnormalities are presented in table II.

In physical examination in 36 (23.08%) cases hepatomegaly was observed, in nine patients coexisting with splenomegaly. In 8 cases enlargement of spleen without hepatomegaly was noticed. Ascites was observed in 9 patients, encephalopathy – in 5 (3.21%).

Thirty five (22.44%) patients had a family history of WD. The initial alanine transaminase (ALT) activity was 183.8±136.8 (6-676) and aspartate transaminase (AST) activity was 110.6±77.1 (20-430). Isolated elevated serum aminotransferases (with bilirubin <2 mg/dl and INR <1,5) was noticed in 97 (62.18%) cases.

Table I. Ferenci scoring system.
Tabela I. Skala Ferenci.

Kayser-Fleischer ring *Pierścień Kayser-Fleischer*	Present *Obecny*	2
	Absent *Brak*	0
Neurologic involvement *Objawy neurologiczne*	Severe *Poważne*	2
	Mild *Łagodne*	1
	Absent *Brak*	0
Serum ceruloplasmin *Poziom ceruloplazminy*	>0.2 g/l	2
	0.1-0.2 g/l	1
	<0.1 g/l	0
Coombs negative hemolytic anemia *Anemia hemolityczna (Coombs-negatywna)*	Present *Obecna*	1
	Absent *Brak*	0
Liver copper *Miedź w bioptacie wątroby*	>5xULN (250 µg/g) *>5xGGN (250 µg/g)*	2
	50-250 µg/g	1
	Normal (<50 µg/g) *Prawidłowy (< 50µg/g)*	-1
	Rhodanine stain – present *Dodatnie barwienie na rodaninę*	1
Urinary copper excretion *Wydalanie miedzi z moczem*	Normal, but >5x ULN after penicillamine *Prawidłowy, ale >5x GGN po penicylaminie*	2
	>2x ULN *>2x GGN*	2
	1-2x ULN *1-2x GGN*	1
	Normal (<0.9 µmol/d or <100 mg/d) *Prawidłowy (<0.9 µmol/d lub <100 mg/d)*	0
Mutation analysis *Badanie molekularne*	2 chromosomes mutations *Mutacje na 2 chromosomach*	4
	1 chromosome mutation *Mutacja na 1 chromosomie*	1
	No mutation detected *Nie wykryto*	0

UNL – Upper Normal Limit
GGN – Górna Granica Norma

Diagnosis

From 154 tested patients in 139 (90.26%) cases ceruloplasmin serum concentration was ≤0,2 g/l, in 56 (36.36%) - ≤0,1 g/l. Basal urinary copper excretion was tested in 146 patients and in 51 patients the levels were between 50 and 100 µg/24 h, 81 patients had levels >100 µg/24 h, highly suspicious for WD. Genetic analysis was performed in 155 (99.36%) cases. In 284 out of 310 alleles we detected disease causing mutations. The most common mutation was p.H1069Q mutation, in 72 patients compound heterozygosity and in 58 patients homozygosity was revealed. p.A1135fs was the second common mutation which was detected in 26 alleles (homozygosity was revealed in 4 cases), the third one – p.Q1351X – in 10 alleles (homozygosity – in 1 case). In 18 patients only one mutation was identified. Scoring system for diagnosis WD according to Ferenci et al. is illustrated in table I. Diagnosis of WD was done on the basis of presence of a score of 4 or more.

DISCUSSION

This study is description one of only a few large cohorts of pediatric patients with Wilson's disease reported so far. Some studies reported a predominance of males [5, 6] while other [7-9] reported female predominance. In our study female constituted the majority of our patients (55.1%).

Table II. Clinical presentation.
Tabela II. Obraz kliniczny.

Hepatic features ***Manifestacja wątrobowa***	**Number of patients** ***Liczba pacjentów***	**%**
Hepatitis *Zapalenie wątroby*	122	78.2
Liver failure (acute/exacerbation of chronic) *Niewydolność wątroby (ostra/zaostrzenie przewlekłej)*	25	16.03
Psychiatric features ***Objawy psychiatryczne***	**Number of patients** ***Liczba pacjentów***	**%**
Depresion *Depresja*	3	1.92
Attention Deficit Hyperactivity Disorder *Zespół nadpobudliwości z deficytem uwagi*	1	0.64
Comprehensive behavioral disorders *Całościowe zaburzenia zachowania*	1	0.64
Neurological features ***Objawy neurologiczne***	**Number of patients** ***Liczba pacjentów***	**%**
Dysarthria *Zaburzenia mowy*	3	1.92
Drooling *Ślinotok*	1	0.64
Dystonia *Dystonia*	1	0.64
Spasticity *Spastyczność*	1	0.64
Tremor/epilepsy *Drżenia/padaczka*	3	1.92

Wilson disease is rarely found before 5 years of age though there are single reports of occurrence of disease in younger children [10]. From all 156 patients in this study the diagnosis was confirmed in 13 cases before the age of 5 years. Moreover, 5 patients presented with elevated aminotransferases activity at the age of 2 years.

WD has a wide spectrum of clinical presentation at any age with variable hepatic as well as neuropsychiatric symptoms. Therefore, it must be sought in any child with undiagnosed evidence of liver dysfunction [11, 12]. Establishing the diagnosis is straightforward if the major clinical and laboratory features are present: neurological symptoms and signs, Kayser-Fleischer rings, low serum ceruloplasmin concentrations, increased urinary copper excretion and liver parenchymal copper concentration. The hepatic presentation is varied. Children may be asymptomatic and elevation of aminotransferases activity may be an incidental finding [13]. Sometimes splenomegaly due to portal hypertension may be the only finding [14]. Moreover, acute liver failure or cirrhosis may be one of the presentations of WD [15].

Neuropsychiatric features usually develop in adult but may occur in children. Early neurological features are behavior abnormalities, deterioration of school performance or difficulties in activities requiring hand-eye coordination [16]. Other neurological manifestations include deterioration of handwriting, drooling, dysarthria, dystonia, and spasticity. Psychiatric disorders may be the dominant in up to 20% of adult patient [17]. Adolescents may experience an unexplained deterioration in schoolwork, as well as severe depression or various neurotic behavior patterns [17]. Common psychiatric abnormalities are depression, anxiety or even frank psychosis [18]. In Kleine et al. analysis of Brazilian children 10.8% of patients presented neurological symptoms with hepatosplenomegaly. [19]. In clinical description of 100 pediatric patients from Bangladesh neurological features were noticed in 6% cases and 14% manifested both hepatic and neurological disease [20]. In our study 94.23% had only hepatic involvement and only 6.4% patients had neuropsychiatric presentation all of them accompanied by hepatical features. This prevalence of liver disorders is higher than the 80% reported by El-Karaksy et al. [21]. High prevalence of liver features may be explained by the age of study group. Moreover, the study was conducted at Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics where most of the patients come with hepatic complaints. Furthermore, neurological presentation and encephalopathy were evaluated separately.

Early detection of WD is important in order to avoid disease progression. In 2001 Ferenci et al. proposed a diagnostic scoring system based on clinical, biochemical,

histological and molecular findings [3]. Niscado et al. confirmed that WD scoring system maybe a reliable tool also in children with a mild liver disease [22]. Authors demonstrated that in children the best WD diagnostic threshold of ceruloplasmin is 20 mg/dl. On contrary Dhawan et al. reported that up to 20% of pediatric and also adult WD patients show normal ceruloplasmin level [23]. However most patients (90.26%) in this study had ceruloplasmin serum level below 20mg/dl, similarly to previous reports [5, 21]. Another test useful for diagnosis for WD is basal urinary copper excretion (CuB). It has been suggested that diagnosis of WD in children should be considered when this test yields the value >40 μg/24 h [24] and the level diagnostic for WD should be > 100 μg/24 h. In the literature up to 19% of WD patients were reported to present with urine copper values below this cutoff value. In our study CuB was tested in 146 patients and in 49 (33.6%) cases the levels were between 50 and 100 μg/24 h and 83 (56.8%) had levels diagnostic for WD. Serum copper level has been proposed as a diagnostic test [25], but it is no longer considered to be a reliable diagnostic tool as it may be low in asymptomatic cases (because ceruloplasmin is low) or high in cases with active liver disease (because free copper is raised).

Presence of KF rings are reliable sign in WD but it may also be found in chronic active hepatitis, primary biliary cirrhosis, chronic cholestasis and cryptogenic cirrhosis. El-Karaksy et al. reported 33% children with liver disease and 62.5% with neurological presentation [21]. In our study Kayser-Fleischer ring was noticed in 7 (4,5%) cases – in 5 patients with liver disease and in 2 with both hepatic and neurological symptoms.

To date, about 800 different mutations described within the *ATP7B* gene have been reported in the Human Gene Mutation Database HGMD® [26]. P.H1069Q is so far the most common mutation in central Europe, accounts for frequencies about 30-60% in series of patients from Poland, Romania, Austria, Saxony and other central European countries [27-30]. Detection of mutations on both chromosomes allows a definitive diagnosis of WD, whereas it cannot be excluded because of their absence. Since other mutations occur, patients require genetic screening of the entire gene, however, selected exons are chosen for initial screening according to the population group. Vrabelova et al. reported that screening of five prevalent mutations in patients from the Czech and Slovakia detected 70% of WD alleles [31]. In our study mutation analysis was performed in 155 cases in presented cohort confirming that the common mutation was p.H1069Q mutation. Therefore, genetic screening is especially supportive in pediatric cohorts and enables eventually the screening of relatives.

Limitation of our study is a retrospective analysis. We used Ferenci score system since 2001 but all the tests according to Ferenci were also performed in previous years and finally allowed to confirm the diagnosis.

Strength of our study is a very huge cohort of pediatric patients, the largest one from a single center. We admitted children from all over the country which allow us to conclude on the whole Polish pediatric patients. Furthermore, we used the same diagnostic approach over the years.

CONCLUSIONS

Wilson disease can present with only significantly increased transaminases activity and hepatomegaly, but in some cases the first symptoms can be liver failure. Neurological symptoms are very rare in children. Diagnostic approach is challenging due to wide spectrum of clinical presentations in a high variable degree of severity and there is no single diagnostic test that can exclude the disease with certainty. Wilson disease should be regarded in any child with evidence of liver dysfunction, using all diagnostic tests including molecular analysis, still ceruloplasmin and urinary copper excretion can be used as the first tests as they have high sensitivity.

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Author's contributions/Wkład Autorów
Socha P designed the study; Naorniakowska M was responsible for the review of the literature, interpretation of data and initial preparation of the paper; Dądalski M, Kamińska D, Jańczyk W, Lebensztejn D, Fyderek K and Wysocki J were involved in collecting the data and editing the manuscript; Socha P prepared final version of the manuscript.

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