

## THE DELAY OF THE DIAGNOSIS IN WILSON'S DISEASE

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### Abstract

**Aims.** To study the factors which influence the delay of Wilson's disease (WD) diagnosis.

**Patients and methods.** We analyzed retrospectively the medical documents of 21 patients suffering from Wilson's disease. The diagnostic score (Ferenci et al. - Liver International 2003) was calculated. The patients were tested for mutations known to cause WD (by semi-nested PCR for H1069Q mutation, followed by sequencing of the exons 3 to 21 - Prof. Ferenci - Vienna) and classified as follows: homozygous, compound heterozygous, heterozygous and negative for the mutations. We studied the relation between the delay of the diagnosis and the clinical and laboratory variables.

**Results.** Sex ratio was F/M = 10/11; 5 patients were adults and 16 pediatric. We found statistically significant correlations with the diagnostic delay for the following: age ( $p=0.015$  – numerically and  $p=0.007$  dichotomically – pediatric/adult), family screening ( $p=0.027$ ), hepatic involvement ( $p=0.004$ ) and psychiatric manifestations ( $p=0.028$ ). The genetic status did not influence the diagnostic delay ( $p=0.113$ ) and neither did other parameters.

**Conclusions.** WD is diagnosed faster in the pediatric population (probably the effect of a higher clinical suspicion) and in patients showing hepatic manifestations; the presence of psychiatric manifestations supplementary delays the diagnosis. The presence of the genetic mutations does not shorten the diagnostic delay.

**Keywords:** Wilson's disease, rare diseases, delayed diagnosis.

## ÎNTÂRZIEREA STABILIRII DIAGNOSTICULUI DE BOALĂ WILSON

### Rezumat

**Obiective.** Studiul factorilor care influențează întârzierea stabilirii diagnosticului de boală Wilson (BW).

**Pacienți și metodă.** Am analizat retrospectiv documentele medicale ale 21 pacienți cu BW. Am calculat scorul de probabilitate diagnostică (Ferenci et al. - Liver International 2003). A fost efectuată analiza mutațiilor cunoscute din BW (H1069Q prin semi-nested PCR, apoi secvențarea exonilor de la 3 la 21 - Prof. Ferenci - Viena) și pacienții au fost clasificați astfel: homozigoți, heterozigoți compuși, heterozigoți și fără mutații cunoscute. Am studiat relația între întârzierea stabilirii diagnosticului și unii parametri clinici și de laborator.

**Rezultate.** Sex ratio a fost F/M = 10/11; 5 pacienți au fost adulți și 16 pediatrici. Am constatat corelații semnificative statistic, cu întârzierea stabilirii diagnosticului pentru următoarele: vârstă ( $p=0.015$  – numeric și  $p=0.007$  dihotomic – pediatric/adult), depistarea la membrii familiei ( $p=0.027$ ), afectarea hepatică ( $p=0.004$ ) și manifestările psihiatrice ( $p=0.028$ ). Statusul genetic și alți parametri nu au influențat întârzierea diagnosticului ( $p=0.113$ ).

**Concluzii.** BW este diagnosticată mai repede la populația pediatrică (probabil

*efectul unei suspiciuni clinice mai mari) și la pacienții cu afectare hepatică; prezența manifestărilor psihice întârzie suplimentar diagnosticul. Prezența mutațiilor genetice nu reduce întârzierea diagnosticului.*

**Cuvinte cheie:** boală Wilson, boli rare, diagnostic tardiv.

## Background

Wilson's disease (WD), also called "hepatolenticular degeneration", is a rare genetic, autosomal recessive disease, consisting of copper overload in certain tissues, mainly in the liver, brain and cornea [1,2,3]. The disease affects about 30 persons in 1 million [4,5]. The condition is caused by mutations in the ATP7B gene, located on the 13<sup>th</sup> chromosome. As a consequence of the genetic mutations the bile elimination of copper is deficient [6,7]. There are 3 main types of clinical manifestations: neurologic and/or psychiatric, hepatic and ocular; other organs may be also involved (kidney, bones and joints, heart, pancreas) [3,7,8,9]. The rarity of the disease and the polymorphism of its manifestations make the diagnosis a difficult one, usually looked for after other diseases are ruled out [10]. In order to overcome the difficulty of the diagnosis Ferenci et al. proposed a scoring system based on the main clinical, biochemical, neuroimaging and genetic features of WD, providing an estimate of the likeliness of a patient to actually have the disease [11]. If the diagnosis is set soon there is less damage of the organs by the copper deposits, the treatment is more efficient and the patients have a better prognosis. The usefulness of the diagnosis of WD in the pre-symptomatic stage in the siblings of a symptomatic patient is well established, with benefic consequences on the outcome [12,13,14,15]. Despite the progress in the investigations there is still a delay of the diagnosis of WD. The quantification of the diagnostic delay in a symptomatic patient and the evaluation of the factors which influence it have been studied by several authors [16,17,18]. The main causes seem to be the low clinical awareness and the polymorphism of the manifestations [16]. The delay is shorter for patients with a hepatic presentation of WD than for those having a neurological presentation [18]. Data concerning the issue of the diagnostic delay are lacking in the medical literature in our country so far.

## Aims

We aimed to evaluate the magnitude of the delay of the diagnosis of WD and the factors which influence it.

## Patients and methods

We analyzed retrospectively the medical documents of 21 patients suffering from Wilson's disease, consulted and/or hospitalized in the 5<sup>th</sup> Medical Clinic (the adults – defined as aged 18 or more) and in the 2<sup>nd</sup> Pediatric

Clinic (the pediatric patients – defined as aged under 18) in Cluj-Napoca, Romania between January 2003 and February 2010. The neurological examination was realized in the Neurological Clinic (the adults), respectively in the Children Neurological Clinic (the pediatric patients). The patients underwent slit-lamp ophthalmologic examination, looking for Kayser-Fleischer (KF) ring, either in the Ophthalmologic Clinic (affiliated to "Iuliu Hațieganu" University of Medicine and Pharmacy), or in an outpatient clinic in Cluj-Napoca. The patients were tested for mutations known to produce WD: the rapid method for the detection of H1069Q mutation was done first in all patients (semi-nested PCR); the samples of the patients who were not homozygous for H1069Q mutation underwent sequencing of the exons 3 to 21 by DNA-denaturing and HPLC. The genetic testing was done by Prof. Ferenci and his co-workers of Innere Medizin III – Vienna Medical University.

Clinical, laboratory and genetic data were recorded. The clinical data comprised: approximate date of the first symptoms (as the patient could recall, after pertinent explanations from the examining physician), onset modality (hepatic, neurologic or family screening – if the patient was diagnosed by active screening consecutively to WD diagnosed in a symptomatic sibling). The presence and the severity of hepatic involvement, the presence of neurologic and psychiatric manifestations were noted. The result of the slit-lamp examination was recorded as: KF ring absent/unilateral/bilateral. Consequently each patient was attributed to one of the phenotypes defined by Ferenci et al. [11].

Laboratory data relevant for our study were recorded: ceruloplasminemia, 24 hours-cupruria, and serum copper (cupremia). The results of the genetic testing assigned the patients to one of the following groups: homozygous (for a known mutation), compound heterozygous (2 different mutations), heterozygous (mutation on one chromosome, no known mutation on the other) and negative for known mutations.

The diagnostic score also defined by Ferenci et al. was calculated using the clinical, laboratory and genetical parameters [11].

The most important variable for this study, the diagnosis delay, was automatically calculated by the computer by subtraction of the approximate date of the first symptoms from the date of a WD disease diagnosis. The result was expressed in days.

We tested the diagnosis delay for statistical correlations with all the above-mentioned parameters. We performed Mann-Whitney, Kruskal Wallis and Chi-square tests accordingly. We used SPSS 14 software for Windows.

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## Results

In the group of 21 WD patients we studied, the sex ratio was F/M = 10/11. The average age was 19.47 years and the median 14 years, ranging from 8 to 55 years. 4 patients were adults and 17 pediatric patients.

The diagnosis delay ranged from 0 days (the diagnosis was set the day the patient was consulted/hospitalized) to 3288 days (approximately 9 years), with an average of 812.14 and a median of 120 days.

There was no correlation between sex and the diagnostic delay ( $p=0.774$ ).

Age at diagnosis was tested for correlation with the diagnosis delay in 2 different ways: as a number (expressed in years) and as a dichotomic variable (pediatric/adult). Both ways of testing rendered significant correlations, greater was the age at diagnosis longer the diagnosis delay was (results in table I). The most striking difference is noticed in the dichotomic approach: the average delay is 482.88 (approximately 1 year and 4 months) days for the pediatric sub-group and 1865.8 days (approximately 5 years and 1 month) for the adults.

By classifying the onset modalities of WD in neurological, hepatic and family screening, we found a significant difference among the three ( $p=0.002$ ). By subdividing the group in patients diagnosed by screening and patients diagnosed due to symptoms there is also a significant difference in the delay ( $p=0.027$ ,  $r=-0.481$ ), which corresponds to the definition of screening itself.

**Table I.** The relation between the clinical data and the diagnosis delay.

Clinical parameter	p value	Coefficient of correlation
Sex	0.774	-
Age (numeric - years)	0.015	0.524
Age (dichotomic - pediatric/adult)	0.007	0.574
Hepatic involvement	0.004	-0.602
Hepatic disease severity (cirrhosis/chronic hepatitis)	0.690	-
Neurological manifestations	0.083	-
Psychiatric manifestations	0.028	0.480
Kayser-Fleischer ring (absent/present)	0.798	-
Clinical phenotype	0.330	-
Diagnostic score (Leipzig)	0.961	-

The presence of hepatic involvement shortened the diagnosis delay ( $p=0.004$ ,  $r=-0.602$ ). In the sub-group of 17 patients displaying hepatic manifestations, the severity of the hepatic disease (cirrhosis/chronic hepatitis) did not influence significantly the magnitude of the diagnosis delay ( $p=0.690$ ). The presence of neurological manifestations did not influence the delay ( $p=0.083$ ) and neither did the presence of KF ring ( $p=0.798$ ). On the contrary, the presence of psychiatric manifestations did influence the diagnostic delay ( $p=0.028$ ), but in the wrong direction, by prolonging it ( $r=0.480$ ).

One of the main targets of our study was to check if one of the clinical phenotypes described by Ferenci et al. is

diagnosed easier, in a shorter period of time. We assigned therefore our patients to H1 (acute liver disease), H2 (chronic liver disease), N1 (neurologic associated with liver disease), N2 (neurologic not associated with liver disease), Nx (neurologic, liver disease not investigated at diagnosis), O (others) (results in table II). There was no difference among all these sub-groups of patients concerning the diagnosis delay (result in table I). The diagnostic probability score (Leipzig score, as it is named in some papers), defined by the same authors, did not correlate with the diagnosis delay either (see table I).

**Table II.** The distribution of patients on clinical phenotypes.

Phenotype code	Phenotype definition	Number of patients
H1	acute liver disease	3
H2	chronic liver disease	9
N1	neurologic associated with liver disease	4
N2	neurologic not associated with liver disease	3
Nx	neurologic, liver disease not investigated at diagnosis	2
O	others	0

The laboratory values did not correlate significantly with the diagnosis delay (results in table III).

**Table III.** The relation between the laboratory and genetic data and the diagnosis delay.

Parameter	p value
Ceruloplasminemia	0.394
Cupremia	0.879
Cupruria	0.155
Genetic status	0.113

According to the results of the genetic testing we classified our patients in: homozygous (for a mutation known as causative of WD), compound heterozygous (2 different mutations known as causative of WD), heterozygous (known mutation on one chromosome, no known mutation on the other) and negative for known mutations (see table IV). There was no statistically significant difference among the 4 sub-groups concerning the diagnosis delay.

**Table IV.** The distribution of patients according to genetic status.

Genetic status	Number of patients
homozygous	9
compound heterozygous	3
heterozygous	1
negative for known mutations	8

## Discussions

The diagnosis delay is maybe the most dangerous thing about WD, as it prevents a patient to receive the proper treatment and it allows the formation of organs' damage. The extreme case, of a patient undetected by family screening is reported by Mak et al. [20]. 18 years after a lapse of screening (genetic testing not available)

the patient presents in end-stage liver disease necessitating liver transplantation. A similar case of delay despite the liver biopsy (unfortunately without determination of copper concentration, only Rhodanine staining which came out negative) is reported by Kok et al. [20]. The diagnosis delay not only it jeopardizes the patient physically, but it also jeopardizes the image of the medical corpus and negatively influences the perception of the disease by the patient [21].

One thing we should underscore about our study is the difficulty to give a good estimation of the diagnosis delay as the moment of first symptoms is hard to locate precisely, but the foreign authors must have had the same problem.

In our group the diagnosis was set after an average delay of 812 days (almost 2 years and 3 months), with a great range, from 0 days to 3288 days (approximately 9 years), results which are concordant with those of researchers in other countries. The average delay ranges in the international literature from 12.8 months to 2 years [16,17,18]. In a study from an expert center the delay ranges from 0 to 360 months [18]. The broad spectrum of wrong diagnoses is also impressive, in all the domains involved: hepatology (confusion with other etiologies of chronic hepatitis), neurology, psychiatry, rheumatology (flat feet) [16,17]. We did not analyze this matter, though it could reveal interesting aspects.

Our finding that hepatic involvement shortens the diagnostic delay is also concordant with the results of other researchers [18]. We did not find articles to state that the presence of psychiatric manifestations supplementary delayed the diagnosis, though it is well known that physicians need great patience and attention in front of such patients.

Neither assignment to a particular phenotype as defined at Leipzig consensus [11], nor the diagnosis score influenced in a statistically significant manner the delay of the diagnosis. This does not make these clinical instruments less valuable, considering the polymorphism of this disease's manifestations, but, as other authors state, early diagnosis of WD greatly relies on clinical awareness. Not even genetics can substitute clinical awareness, as one would never order a genetic testing without thinking first of a particular genetic disorder. We consider that the pediatricians have a greater awareness in the direction of rare disease than the physicians who consult mainly adults, as most of the rare diseases reveal during childhood and our results are in favor of our hypothesis.

### Conclusions

WD is diagnosed in a shorter delay in the pediatric population (probably the effect of a higher clinical suspicion) and in patients showing hepatic manifestations; the presence of psychiatric manifestations supplementary delays the diagnosis. The presence of the genetic mutations does not shorten the diagnostic delay.

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### References

1. Grigorescu-Sido P, Boala Wilson. In: Grigorescu M (ed). *Tratat de hepatologie*. București: Editura Medicală Națională, 2004, 672-678.
2. Sternlieb I, Scheinberg IH. Wilson's Disease. In: Schiff L, Schiff ER (eds). *Diseases of the Liver*. Philadelphia: JB Lippincott Company, 1993, 659-668.
3. Sherlock S, Dooley J (eds). *Wilson's Disease*. In: *Diseases of the Liver and the Biliary System*. Oxford: Blackwell Science Ltd., 1997:417-425.
4. Roberts EA, Schilsky ML. Diagnosis and Treatment of Wilson Disease: An Update. *Hepatology* 2008;47:2089-2111.
5. Brewer GJ, Askari FK. Wilson's disease: clinical management and therapy. *Journal of Hepatology* 2005;42:S13-S21.
6. de Bie P, Muller P, Wijmenga C, et al. Molecular pathogenesis of Wilson and Menkes disease: correlation of mutations with molecular defects and disease phenotypes. *J. Med. Genet.* 2007;44:673-688.
7. Ferenci P. Review article: diagnosis and current therapy of Wilson's disease. *Aliment Pharmacol Ther* 2004;19:157-165.
8. Gow PJ, Smallwood RA, Angus PW, et al. Diagnosis of Wilson's Disease: An Experience over Three Decades. *Gut* 2000;46:415-9.
9. Shanmugiah A, Sinha S, Taly AB, et al. Psychiatric Manifestations in Wilson's Disease: A Cross-Sectional Analysis. *J Neuropsychiatry Clin Neurosci* 2008;20:81-85.
10. Ala A, Walker AP, Ashkan K, et al. Wilson's disease. *Lancet* 2007;369:397-408.
11. Ferenci P, Caca K, Loudianos G, et al. Diagnosis and phenotypic classification of Wilson disease. *Liver Int* 2003;23:139-142.
12. Levi AJ, Sherlock S, Scheuer PJ, et al. Presymptomatic Wilson's disease. *Lancet* 1967;2:575-579.
13. Arima M, Komiya K, Fujisawa A, et al. Prevention of Wilson's disease in asymptomatic patients. *Proc Aust Assoc Neurol.* 1968;5:197-201.
14. Sternlieb I, Scheinberg IH. Prevention of Wilson's disease in asymptomatic patients. *N Engl J Med.* 1968;278:352-359.
15. Wu ZY, Lin MT, Murong SX, Wang N. Molecular diagnosis and prophylactic therapy for presymptomatic Chinese patients with Wilson disease. *Arch Neurol.* 2003;60:737-741.
16. Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. *J Neurol Neurosurg Psychiatry* 1992;55:692-696.
17. Prashnath KL, Taly AB, Sinha S, et al. Wilson's disease: diagnostic errors and clinical implications. *J Neurol Neurosurg Psychiatry* 2004;75:907-909.
18. Merle U, Schaefer M, Ferenci P, et al. Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut* 2007;6:115-120.
19. Mak CM, Tam S, Fan ST, Liu CL, Lam CW. Wilson's disease: a patient undiagnosed for 18 years. *Hong Kong Med J.* 2006;12(2):154-8.
20. Kok KF, Hoevenaars B, Waanders E, et al. Value of molecular analysis of Wilson's disease in the absence of tissue copper deposits: a novel ATP7B mutation in an adult patient. *Neth J Med* 2008;66:348-350.
21. Huyard C. What, if anything, is specific about having a rare disorder? Patients' judgements on being ill and being rare. *Health Expect.* 2009;12:361-370.