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PHENOTYPIC AND GENOTYPIC DIAGNOSIS OF WILSON'S DISEASE: A CLINICAL CASE

Cumpata Veronica[1], Turcanu Adela[1], Tcaciuc Eugen[1]
[1]Discipline of Gastroenterology, Department of Internal Medicine, "Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
Autor corespondent:Cumpata Veronica; e-mail: veronica.cumpataciorba@gmail.com

Summary

Wilson's disease is a rare genetic disease determined by a mutation of the ATP7B gene, which leads to reduced biliary excretion of copper and its storage in various tissues. Although it is a monogenic disorder, the disease is characterized by extraordinary clinical and genetic diversity. The given article tells about a young man diagnosed with Wilson's disease. The patient was evaluated according to international protocols: clinical, hematological, biochemical, ophthalmological, imaging, endoscopic and genetic. Thus, according to the results of all investigations, a Leipzig score ≥ 4 points was established, which is valid for a definite diagnosis of Wilson's disease. The peculiarities of this clinical case are the early onset of the disease with primary manifestations of advanced liver disease, the delay in establishing the diagnosis, the compound heterozygous status, the low compliance of the patient, and the refusal to accept the presence of a genetic disease by the family.

Keywords: *Wilson's disease, phenotype, genotype, compound heterozygous.*

Rezumat

Diagnosticul fenotipic și genotipic al bolii Wilson: caz clinic.

Boala Wilson reprezinta o maladie genetica rară determinata de o mutația genei ATP7B, ce duce la reducerea excreției biliare a cuprului și depozitarea lui în diferite țesuturi. Deși, este o tulburare monogenică, boala se caracterizează printr-o diversitate clinică și genetică extraordinară. Articolul dat relatează despre un tânar diagnosticat cu boala Wilson. Bolnavul a fost evaluat conform protocoalelor internaționale: clinic, hematologic, biochimic, oftalmologic, imagistic, endoscopic și genetic. Astfel, conform rezultatelor tuturor investigațiilor s-a stabilit un scor Leipzig ≥ 4 puncte, ce este valabil pentru un diagnostic cert de boală Wilson. Particularitățile acestui caz clinic sunt debutul precoce a bolii cu manifestări primare de boală hepatică avansată, întârzierea stabilirii diagnosticului, statutul de heterozigot compus, complianța redusă a pacientului și refuzul de a accepta prezența unei boli genetice de către familie.

Cuvinte-cheie: *boală Wilson, fenotip, genotip, heterozigot compus.*

Резюме

Фенотипическая и генотипическая диагностика болезни Вильсона: клинический случай.

Болезнь Вильсона — редкое генетическое заболевание, определяемое мутацией гена ATP7B, что приводит к снижению экскреции меди с желчью и ее депонированию в различных тканях. Хотя это моногенное заболевание, заболевание характеризуется необычайным клиническим и генетическим разнообразием. В данной статье рассказывается о молодом человеке с диагнозом болезнь Вильсона. Пациент был оценен в соответствии с международными протоколами: клиническим, гематологическим, биохимическим, офтальмологическим, ультразвуковое исследование, эндоскопическим и генетическим. Таким образом, по результатам всех исследований была установлена Лейпцигская оценка ≥ 4 балла, что справедливо для достоверного диагноза болезни Вильсона. Особенностью данного клинического случая является раннее начало заболевания с первичными проявлениями запущенного заболевания печени, задержка в установлении диагноза, компаунд-гетерозиготный статус, низкая комплаентность больного и отказ принять наличие генетического заболевания. семьей.

Ключевые слова*: болезнь Вильсона, фенотип, генотип, компаунд-гетерозиготный.*

Introduction. Wilson's disease (WD) is a monogenic disorder with autosomal recessive transmission caused by a mutation in the ATP7B gene, which disrupts copper metabolism [1]. As a result of the synthesis of a dysfunctional protein, copper accumulates in toxic amounts in various tissues, especially the liver and brain, causing intracellular oxidative injuries with damage to lipids, proteins, DNA and RNA molecules, mitochondria, and finally, the induction of cell apoptosis [2].

WD was first described in 1912 by Dr. Samuel Kinnear Wilson as "progressive lenticular degeneration", a fatal neurological disease with familial transmission associated with chronic liver disease leading to cirrhosis [3]. It is a potentially fatal disorder if not diagnosed and treated early, thus preventing disease progression and the development of irreversible sequelae. Today, WD is one of those rare genetic disorders that benefit from effective lifelong treatment, changing disease prognosis and quality of life in these patients [4].

WD is a globally widespread disorder with a traditionally reported prevalence of 1:30,000 individuals [5], although some research has shown a genetic prevalence of over 1:7026 individuals [6], particularly in socio-culturally isolated communities [7] and in populations with a high risk of inbreeding [8]. In Europe, the clinical prevalence is estimated at 12 – 20:100000 [9]. The age of onset of WD varies from 2 years to 80 years, but most are diagnosed between 5–35 years [5, 9].

WD should be suspected in all adults and children with unexplained liver disease; in all adults with liver disease in combination with a movement disorder or unexplained hemolytic anemia; in all patients between 5-50 years who develop a progressive postural tremor, dystonia, or parkinsonism; in all patients who develop a mixed movement disorder with any red flags and in all patients with an unexplained Coombs-negative hemolytic anemia [10].

Once the diagnosis has been made, the treatment must be lifelong, and its interruption is associated with the progression of the disease and the worsening of the general condition up to acute liver failure [5, 10].

Case report. Male P. C., 34 years old, consulted a hepatologist with the following symptoms: moderate asthenic syndrome, dyspeptic syndrome (reduced appetite, periodic nausea), discomfort in the right hypochondrium during physical activity, hemorrhagic syndrome (weekly episodes of epistaxis and gingivorrhea in quantities small, which stop on their own) in association with the pseudobulbar syndrome (mild dysarthria), extrapyramidal syndrome (tremor of the hands with impairment of writing), cognitive disorders (decreased concentration, attention and memory), instability in walking, emotional lability and periodic headache.

The history of the disease. The patient is considered sick since he was 14 years old when he was admitted to the Mother and Child Institute with decompensated cirrhosis (marked ascites and peripheral edema, severe hypersplenism, maximal cytolysis, hepatoprivation syndrome). Viral, autoimmune and toxic etiology were excluded. Copper metabolism parameters were recommended, but the parents refused to do. Therapy with hepatoprotective, beta-blockers, and diuretics was administered to the improvement of the general condition. Since then, he has been in the family doctor's records, but he did not show up regularly for diagnosis and treatment. In 2014, when he was 26 years old, neurological symptoms such as hand tremors and postural instability were associated. He was consulted by the neurologist and a specific evaluation for WD was insisted upon. Thus it was detected: ceruloplasmin -10.33 mg/dL (22-61), total copper - 37.80 µg/dL (70-150), urinary copper in 24 h - 370 µg/24 h (14.8 - 59.2), the bio-microscopy of cornea - Kayser-Fleischer ring present. The Leipzig score was 4 points. After this, the patient was referred to a geneticist for genetic testing and initiation of chelator therapy. The patient's condition registered an obvious improvement with the initiation of the specific therapy.

Personal medical record. Caucasian race. Moldovan nationality. He is not married, without children.

Family medical record. No sick relatives with liver pathology and/or neuropsychiatric disorders are reported. Brother and sister are reported to be healthy. He does not know the details of intra-family marriage.

Epidemiological record. Occupation – grow flowers. No contact with toxic substances. No allergies. No transfusion. Smoker - 20 cigarettes a day. Occasional alcohol consumption - wine, beer.

Recent examinations. Thrombocytopenia ($67*10^9$/L), mild transaminitis (ALT – 52 U/L, AST – 49 U/L), elevated alkaline phosphatase (135.9 U/L) and gamma-glutamyltransferase (124.90 U/L). Bilirubin, total protein, albumin, and prothrombin were normal. Serological viral marker: HBsAg, anti-HBs, anti-HBcor total, and anti-HCV – negative. Autoimmune markers: ANA, AMA – negative; Ig M, Ig G, Ig A, and Ig E were normal. Tumor markers: alpha-fetoprotein, CEA and CA 19-9 were normal.

The ultrasound of the abdominal organs showed moderate hepatomegaly (163.8*77.4 mm), marked splenomegaly (185.7*67.0 mm), increased size of the portal (13.5 mm), and splenic veins (8.0 mm), during inspiration and expiration, the size of the portal vein does not change. The gall bladder, intrahepatic and extrahepatic bile ducts were normal.

The high digestive endoscopy was performed with a finding of uncomplicated esophageal varices, grade I-II.

Genetic testing by the Sanger sequencing method identified pathogenic mutations on exon 14 - p.H1069Q (c.3207C>A) and on exon 20 - p.G1341D (c.4022G>A) of compound heterozygous type.

The patient is currently waiting for liver elastography and cerebral magnetic resonance.

The clinical diagnosis: Wilson's disease, clinically defined and genetically confirmed (p.H1069Q/p.G1341D), neuro-hepatic phenotype (N1- Ferenci classification). The Leipzig score - 8 points. Clinical form: liver cirrhosis, active phase, compensated stage, slow-progressive evolution, Child-Pugh A score (5 points) in association with the pseudobulbar, extrapyramidal syndrome, and cognitive disorders. Secondary thrombocytopenia to the underlying pathology.

Treatment. It was recommended to have a low-copper diet, drink water with a verified amount of

copper, use copper-free cookware and utensils, avoid drinking alcohol, quit smoking, and take medications or supplements only as directed by a doctor to avoid copper overload.

The specific medication recommended for administration includes D-penicillamine 250 mg, 2 tablets t.i.d., 1 hour before meals; Pyridoxine 25 mg, 2 tablets q.d., throughout the administration with D-penicillamine; Zinc sulfate 124 mg, 1/2 tablets b.i.d., 30 min before the meal or 2 h after the meal. In addition, standard care therapy for a patient with chronic liver disease was recommended.

The subject is monitored by a hepatologist, neurologist, and geneticist. Unfortunately, the patient does not always follow the general recommendations, consumes alcohol 1-2 times a week (0.5-1 l of beer or 0.3-0.5 ml of wine), smokes, and sometimes forgets to administer the chelating agents. Family members cannot influence his lifestyle and sometimes remain indifferent to doctors' indications.

Discussion. WD occurs with an extraordinary phenotypic and genotypic diversity, which makes it difficult to define the diagnosis. Due to the multisystemic involvement (hepatic, cerebral, cardiac, osteoarticular, endocrine, ocular), the manifestations are often subtle and can mimic other diagnoses [4]. To facilitate the establishment of the diagnosis, the Leipzig score was proposed (April 2001), which represents an important tool in the evaluation of the suspect subject for WD. It includes clinical, hematological, biochemical, histological, and genetic data; and a score ≥ 4 points allows us to confirm the diagnosis. The phenotypic classification of WD (Ferenci classification, 2001) distributes the patient in the group with the predominantly affected organ, as well as allows us to identify the primary manifestations of other associated clinical symptoms over time [11]. The patient described in the article belongs to group N1 - neurological presentation associated with symptomatic liver disease. In this situation, the patient usually has cirrhosis of the liver at the time of diagnosis of neurological WD. Chronic liver disease may precede the onset of neurological symptoms for several years.

The clinical expression of the WD is very diverse, ranging from totally asymptomatic subjects to patients with severe liver disease and with an unpredictive relationship between liver severity disease and classic neurological patterns. The symptoms can occur at any age, but primary liver lesions are most frequently encountered in adolescence, manifesting as an advanced chronic liver disease [6, 12], as happened in the presented case. The hepatic presentation precedes the onset of neurological symptoms by as much as 10 years, which highlights that neurological signs may be subtle and easily missed by patients and specialists [13]. In our patient, the neurological symptoms were diagnosed 12 years after the first liver manifestation and served as a reason for the diagnosis of WD.

There is no pathognomonic clinical sign or a single specific test for diagnosis, a series of tests must be used and the results obtained should be framed in a clinical, biochemical, and genetic context [5]. To increase diagnostic accuracy, WD must be differentiated from hepatitis of other etiologies such as viral (B, C, D), autoimmune, primary biliary cholangitis, primary sclerosing cholangitis, drug-induced liver injury, nonalcoholic or alcoholic steatohepatitis, hemochromatosis, deficiency alpha 1 antitrypsin and ischemic liver damage [14]. Also, the primary neurological manifestations or those associated along the way need to be differentiated from other Wilson-like neurological pathologies, depending on the syndrome present in the patient (multiple sclerosis, Parkinson's disease, Huntington's disease, etc.) [15].

When WD is suspected, it is necessary to perform a set of targeted examinations: parameters of copper metabolism (serum ceruloplasmin, total serum copper, urinary copper in 24h); eye control by an experienced ophthalmologist to identify the Kayser-Fleischer ring or other changes described in this disease; liver biopsy to quantify copper in liver tissue and a genetic test to detect mutations in the Wilson gene [5].

Suggestive values for WD include low level of the ceruloplasmin (typically <0.1 g/L, but can be <0.2 g/L); low serum copper and high 24-hour urine copper (> 1.6 μmol/24 h (100 μg/24 h) or > 0.64 μmol/24 h in children/asymptomatic siblings) [1, 10]. In some cases, the values of copper metabolism parameters can be influenced by the presence of conditions such as chronic cholestasis, acute inflammation, hyperestrogenemia, healthy heterozygotes, administration of certain drugs, increased absorption of zinc, incorrect collection of samples, and in inappropriate containers, other rare genetic disorders or overestimated by immunological tests. Therefore, copper findings must be interpreted interdependently with other clinical and genetic modifications to avoid false results [5, 15].

The Kayser-Fleischer ring occurs in 95% of patients with a neurological phenotype, 50% in those with liver damage, and 20-30% in presymptomatic/asymptomatic ones [5, 10]. The evaluation of the eye is a complex one and includes all the ocular structures, including the movement of the eyeball, thus it is possible to identify other changes, such as sunflower-type cataract, reduced eye mobility, apraxia of eyelid opening, loss of accommodation response [16].

Quantification of copper in dry liver tissue is one of the specific tests for confirming WD, and a result of> 4 μmol/g or ≥ 250 μg/g in the absence of cholestasis is considered the hallmark of WD. Although it is an important diagnostic test, its performance is recommended in uncertain clinical cases due to the complications that may occur, the associated cost, as well as the need for special instruments and devices. It is performed only in specialized centers [5]. Our patient did not conduct such an investigation.

Carrying out an imaging examination (abdominal ultrasonography, magnetic resonance, or computed tomography), endoscopic evaluation, and assessment of the degree of fibrosis can help in confirming and staging the disease, to prevent complications and irreversible sequelae [5, 10].

In the case of a subject with a clinically definite WD diagnosis, the molecular-genetic test is not mandatory but provides direction in the process of guiding the screening of relatives. Also, knowing the mutational status is important in identifying the genotype-phenotype correlation depending on sociodemographic and epidemiological indices, clinical and paraclinical data [17]. In the patient described in this article, 2 compound heterozygous mutations were identified - p.H1069Q/p.G1341D.

p.H1069Q (c.3207C>A) represents the most known pathogenic mutation located in exon 14, with allele frequency in the general population ranging from 10-40%, and in the European population being 30-70% [9, 18]. It is located in the SEHPL sequence in the N domain resulting from the substitution of histidine → glutamic acid at position 1069 of the ATP7B polypeptide chain [18].

p.G1341D (c.4022G>A) is a likely pathogenic mutation located in exon 20, that occurs in the M domain of ATP7B proteins at the level of the transmembrane channel 7 resulting from the substitution of glycine → aspartic acid at position 4022 of the ATP7B polypeptide chain. This mutation is associated with neurological and hepatic manifestations. It has been reported so far in Albania, Czechoslovakia, Poland, Bulgaria, Serbia, Egypt, and the Mediterranean area [19, 20].

The type of mutation and the affected functional domain of the ATP7B protein set the age of onset and the course of the disease, mutations in important areas are correlated with a severe course, early onset, and a liver-predominant phenotype, and mutations in less important regions of the gene present with late onset and a predominantly neurological or psychiatric phenotype [2]. The N domain is responsible for binding the ATP molecule to the protein ATP7B, and the mutation at the SEHPL motif level (p.H1069Q) has a major impact on disrupting the intracellular copper transport process [2, 18]. Also observed in the presented case, with a severe early onset at the age of 14 and primary hepatic manifestation.

The studies of the genotype-phenotype correlation in WD showed contradictory results. The phenotypic evolution of mutations proceeds differently when it is a homozygous or compound heterozygous mutation, a fact also determined in studies with a large number of Wilson subjects [21]. Research on the Bulgarian WD patients revealed that a homozygous p.H1069Q mutation was associated more frequently with the hepatic presentation and the significantly rarer presence of the Kayser-Fleischer ring than with the compound heterozygous p.H1069Q mutation and other mutations [22]. Although the genetic aspects of the disease have been clarified, the involvement of epigenetic, metabolic, and habit factors (diet, traditions, exposure to toxic environment) may contribute to clinical heterogeneity [1].

According to published data on 120 patients with WD from the Republic of Moldova, the most frequent pathogenic variants identified were p.H1069Q (19.5%, 47/240 alleles) and p.G1314D (7%, 14/200 alleles). All p.G1341D mutations were compound heterozygous with p.H1069Q, which highlights that these sites are important in the evaluation of Moldavian cohorts [23].

Thus, analyzing the previously exposed data and the patient's case, the following can be suggested, that the p.H1069Q/p.G1341D variant correlates with an onset of the disease in childhood with advanced liver disease, the presence of the Kayser-Fleischer ring, and the association of neurological manifestations over 12 years since the onset of the disease. Of course, to establish with certainty the interrelationship between genotype and phenotype in the presence of these types of mutations, detailed studies on a larger cohort of Wilson patients are needed.

The key points of the presented case:

1. Onset at a young age with decompensated liver cirrhosis highlights the impact of the mutation on disease severity.
2. The duration from the first manifestation of the disease until the establishment of the diagnosis was approximately 12 years. Although the evaluation of copper metabolism was recommended from the beginning, the parent's refusal to accept a genetic aspect of this disease led to a delay in the diagnosis and the appearance of signs of extrahepatic toxic accumulation.
3. The identification of compound heterozygous type mutations emphasizes the complexity of the clinical case, considering the mutational variability of WD and the impossibility of

doing additional research on the same type of mutations.

4. The initiation of specific drugs led to the improvement of the evolution and stabilization of the pathogenic process.
5. Low patient compliance, family passivity, alcohol consumption, and smoking are factors that can lead to the worsening of the disease evolution.

Unanswered questions...

What would have been the clinical evolution of this patient if the diagnosis had been established from the age of onset?

What would have been the fate of the neurological manifestations if the therapy with copper chelators was initiated from the beginning?

Conclusions:

The presence of WD should be assumed in any patient with liver pathology of unknown cause, regardless of age.

Early diagnosis and initiation of etiopathogenetic treatment prevent damage to other organs and irreversible changes.

Compliance with the general and therapeutic recommendations of doctors can improve the quality of life and increase life expectancy.

The family has a major impact in providing psycho-emotional support, helping in the care process (preparing free-copper meals, using low-copper cosmetics/detergents, and controlling the water consumed), increasing treatment adherence, monitoring doctor's visits, and training relatives/ friends regarding WD.

The involvement of a multidisciplinary team (family doctor, hepatologist, neurologist, geneticist, and psychologist) ensures adequate care for the patient with WD and valuable support for his family.

Abbreviations

ALT - alanine transaminase; ANA - antinuclear antibodies; AMA – antimitochondrial antibodies; AST - aspartate aminotransferase; ATP - adenosine triphosphate; ATP7B - *copper-transporting ATPase 2;* anti-HBcor tot - hepatitis B core total antibody; antiHBs - hepatitis B surface antibody; anti-HCV sum – *antibody to hepatitis C virus*; b.i.d. - two times a day; CA 19-9 - cancer antigen 19-9; CEA - carcinoembryonic antigen; HBsAg - hepatitis B surface antigen; Ig A - immunoglobulin A; Ig E - immunoglobulin E; Ig G – immunoglobulin G; Ig M – immunoglobulin M; q.d. - a*ntibody to hepatitis C virus*; t.i.d. - three times a day; WD – Wilson's disease.

Conflict of interests. No competing interests were disclosed.

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REACTIVE ARTHRITIS IN A PATIENT AFTER COVID-19 INFECTION: A CASE REPORT AND REVIEW OF THE LITERATURE

Sadovici – Bobeica Victoria, Loghin-Oprea Natalia, Varghese Nevin, Istrati Valeriu, Mazur Minodora
Disciplina medicina internă-semiologie,
Universitatea de Stat de Medicină şi Farmacie „Nicolae Testemiţanu"
Corresponding author: Victoria Sadovici-Bobeică, email: victoria.sadovici-bobeica@usmf.md

Summary

Reactive arthritis in a patient after COVID-19 infection: a case report and review of the literature

COVID-19 infection can lead to a wide variety of complications involving the majority of body systems, including the musculoskeletal one. One of its clinical manifestations of it is reactive arthritis. In the following, we present the clinical case of a 56-year-old woman with post-COVID-19 reactive arthritis and it's follow-up.

***Key words**: reactive arthritis, COVID-19 infection*

Rezumat

Artrita reactivă la un pacient după infecţia COVID-19: raport de caz

Infecţia cu COVID-19 poate duce la o varietate mare de complicaţii care implică majoritatea sistemelor corpului, inclusiv pe cel musculo-scheletal. Una dintre manifestările clinice ale acesteia este artrita reactivă. În cele ce urmează prezentăm cazul clinic al unei femei de 56 de ani cu artrită reactivă post COVID-19 şi monitorizarea acestuia.

***Cuvinte cheie:** artrită reactivă, infecţia COVID-19*

Резюме

Реактивный артрит у пациента после инфекции КОВИД-19: клинический случай

Инфекция COVID-19 может привести к самым разнообразным осложнениям, затрагивающим большинство систем организма, в том числе опорно-двигательный аппарат. Одним из клинических проявлений его является реактивный артрит. Ниже мы представляем клинический случай 56-летней женщины с реактивным артритом после инфекции COVID-19 и его последующее наблюдение.

***Ключевые слова:** реактивный артрит, инфекция COVID-19*