CASE REPORT

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Atypical case of Wilson's disease with psychotic onset, low 24 hour urine copper and the absence of Kayser-Fleischer rings

Atipični primer Vilsonove bolesti sa psihotičnim početkom, niskim bakrom u 24-satnom urinu i odsustvom Kajzer Flajšerovih prstenova

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Abstract

Introduction. Wilson's disease is typically manifested in two clinical forms, neurological and hepatic and in rare cases it starts with psychiatric symptoms exclusively. We presented a rare atypical case of Wilson's disease with psychotic onset. **Case report.** A 22-year-old male patient was initially presented with predominant signs and symptoms of psychiatric disorder and then later with the development of neurological signs and symptoms. Neuroimaging, detected metal deposits in central nervous system (CNS) but not in peripheral organs, while serum analysis excluded pantothenate-kinase associated neurodegeneration and aceruloplasminemia. In favor of the diagnosis of Wilson's disease there were reduced concentrations of copper and ceruloplasmin concentrations and metal deposits in CNS, but other pathognomonic signs and symptoms were absent: increased copper in urine, Kayser-Fleischer rings in Descemet's corneal membrane and deposits of copper in liver. Introduction of penicillamine treatment resulted in improvement in mental and general health of the patient. Molecular genetic analysis definitely confirmed the diagnosis of Wilson's disease. **Conclusion.** Wilson's disease can remain undetected for a long period of time if masked with dominant or exclusive psychiatric symptoms. If clear clinical symptoms and signs, and unambiguous laboratory findings are not present, it is necessary to perform molecular genetic analysis to confirm the definitive diagnosis.

Key words:
hepatolenticular degeneration; diagnosis; mental disorders; copper; molecular biology; genetic diseases, inborn; treatment outcome.

Apstrakt

Uvod. Vilsonova bolest se karakteristično ispoljava kroz dva klinička oblika, neurološki i heparni, a ređe počinje isključivo sa psihijatrijskim simptomima. Prikazan je redak, atipični slučaj Vilsonove bolesti sa psihotičnim početkom. **Prikaz bolesnika.** Muškarac od 22 godine imao je u početku, tokom nekoliko godina, dominantne znakove i simptome psihijatrijskog poremećaja, a tek kasnije neurološke znakove i simptome. Neuroradiološkim analazima su detektovani depoziti metala u centralnom nervnom sistemu (CNS), ali ne i u perifernim organima, a laboratorijskim analizama krvi isključeni su *pantothenate-kinase associated neurodegeneration* i aceruloplazminemija. U prilog dijagnoze Vilsonove bolesti bili su snižena koncentracija bakra i ceruloplazmina u serumu i depoziti metala u CNS-u, ali su bili odsutni drugi patognomonični znaci i simptomi: povišen bakar u urinu, Kajzer-Flajšerovi prstenovi u Descemetovoj membrani korneje i depoziti bakra u jetri. Na terapiju penicilaminom došlo je do poboljšanja psihičkog i opšteg zdravstvenog stanja bolesnika. Dijagnoza Vilsonove bolesti definitivno je potvrđena molekularno genetskim analizama. **Zaključak.** Vilsonova bolest može dugo ostati neprepoznata, ukoliko je maskirana dominantnim ili isključivo psihijatrijskim simptomima. Ako nisu prisutni jasni klinički simptomi i znakovi i nedvosmisleni laboratorijski nalazi, neophodno je uraditi molekularno genetsku analizu radi konačne potvrde dijagnoze.

Ključne reči:
hepatolentikularna degeneracija; dijagnoza; mentalni poremećaji; bakar; biologija, molekulska; nasledne bolesti; lečenje, ishod.

Introduction

Wilson's disease is a progressive autosomal recessive disorder characterized by disruption of transport and excretion, as well as excessive accumulation of copper in liver, eyes, central nervous system (CNS) and other organs. It is clinically manifested in childhood or adolescence, usually before the age of 40, most often in the second decade. Siblings of affected persons have risk of 25% of developing this disease. The name of the disease dates back from 1912, when Alexander Kinnier

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Wilson [1] first described family neurological disorder manifesting with extensive tremor and parkinsonism-like symptoms, all associated with liver cirrhosis. Synonyms for this disease are "hepatolenticular degeneration", "Westphal's pseudosclerosis" and "Strümpel's disease".

Wilson's disease is caused by mutations in the ATP7B gene locus 13q14.3 - q21.1 on the second arm of the 13th chromosome. This gene controls binding of copper for transport protein ceruloplasmin (alpha-2 globulin). Mutations in ATP7B gene change biosynthetic and transporting role of ATPase in cell, resulting in impaired billiary excretion of copper and its accumulation in liver, brain, cornea and other tissues [2]. The disease incidence is estimated to be 1 in 30,000 to 1 in in 50,000 [3, 4], and it is supposed that the prevalence is 30 *per* million, with the frequency of heterozygotous mutations carriers of about 1 in 90 to 1 in 150 [5, 6]. Until now, it has been identified more than 400 mutations in ATP7B gene with characteristic geographic distribution [7, 8]. In a study on Serbian population, molecular gene defect was identified in 80% of alleles of Wilson's disease patients, with 11 different mutations, and the most frequent mutations were H1069Q (48.9% of analyzed alleles), 2304–2305insC (11.4%), and A1003T (5.7%) [9].

Copper is an essential oligoelement absorbed in duodenum, deposited in liver in form of cuproprotein, and in plasma 95% binds to aceruloplazmin, building ceruloplasmin. The remaining 5% of copper binds to albumin and erythrocytes and is excreted through biliary excretion in a form that is not reabsorbed [10, 11].

In cases with a reduced binding of copper for ceruloplasmin which leads to an increase of free circulating copper and its deposit in tissues. The precise nature of biochemical abnormalities is not known, but studies of mitochondrial function indicate the occurrence of free radicals and oxidative stress, due to copper accumulation in mitochondria.

The most common non-neurological manifestations are ocular and hepatic abnormalities. The most prominent ocular sign is Kayser-Fleischer ring – a bilateral green-brown granular deposit of copper in Descement's membrane around corneal limbus which is observed in nearly 100% patients, but not in all [12]. Involvement of the liver leads to chronic liver cirrhosis which can be complicated with splenomegaly, esophageal varices, haemolytic anemia and thrombocytopenia.

The major symptoms of neurological forms of the disease are tremor, dystonia, dysarthria, rigidity, bradykinesia, horeiform dyskinesia and ataxia.

Phenomena associated with this form may be changes in mental status that are often manifested in the form of dementia as a psychomotor retardation, impaired concentration, mnestic deficit, personality disorders, behavioral and affective disorders. Psychotic phenomena, including hallucinations appears very rarely. The psychiatric form of the disease is relatively rare and it is estimated to about 10% of all cases [13–15].

Typical changes in blood laboratory tests point to damage to the functioning of liver and kidneys (aminoaciduria). The levels of serum copper and ceruloplasmin are low: copper < 11 mmol/L (reference values 11.9–20.4 mmol /L), ceruloplasmin < 0.2 g / L (0.2–0.6 g/L), and 24-hour urine copper is increased (finding > 0.1 mg/24 h confirms Wilson's disease, and finding of 0.04 mg/24 h is strongly indicative of Wilson's disease). Liver biopsy reveals cirrhosis and copper deposition. Common findings in computerized tomography (CT) and magnetic resonance imaging (MRI) are cerebrocortical atrophy and the abnormalities in the basal ganglia [15].

The combination of neurological symptoms, Kayser-Fleisher's rings and a low ceruloplasmin level is considered sufficient for the diagnosis of Wilson's disease.

In general, the approach to treatment is dependent on whether there is clinically-evident disease or laboratory or histological evidence of aggressive inflammatory injury, whether neurologic or hepatic, or whether the patient is identified prior to the onset of clinical symptoms. The recommended initial treatment of symptomatic patients or those with active disease is with chelating agents, though there are some reports showing primary treatment with zinc may be adequate for some individuals. The largest treatment experience worldwide is still with D-penicillamine; however, there is now more frequent consideration of trientine for primary therapy [17].

Case report

A male patient, aged 22 was admitted to the Clinic of Psychiatry, Military Medical Academy (MMA), Belgrade, Serbia, after two years of altered behavior in the form of social withdrawal, reduction of verbal communication, increased hostility towards family members, subjective sensation of "vibration" in epigastrium and with occasional verbalization of suicidal ideas. Over the past two years, he was treated as an outpatient in regional psychiatric institution where he was initially diagnosed as adolescent crisis, and was treated with anxiolytics and psychotherapy, and later he was rediagnosed as paranoid schizophrenia, with, prior to hospitalization in MMA, a 12- months-long treatment with atypical antipsychotics (risperidone and clozapine), and antidepressants (paroxetine, mirtazapine, bupropion) and then with typical antipsychotic haloperidol. During outpatient psychiatric treatment, despite the usage of these antipsychotic drugs, there were not any reduction of psychotic phenomena. In that period an electroencephalography (EEG) and transcranial ultrasonography (TCD) were performed – all findings were described as normal. A few months before current hospitalization the patient was in Africa and there he had a brief febrile episode.

On admission, complete physical examination showed practically normal somatic finding: the patient was afebrile, eupnoic, normotensive, cardipulmonally compensated, without the presence of organomegaly. Psychiatric examination revealed changed behavior, hostility, negativism, reduction of verbal communication, poor control of aggressive impulses, proprioceptive hallucinations and excessive sensitivity. Extrapyramidal symptoms – acynetic-rigid syndrome with a significant anteflexion of toes of his left foot were observed by neurological examination. Taking into account that patient had been receiving antipsychotic treatment for one year, extrapyramidal symptoms could be explained as a manifestation of iatrogenic (medicament) parkinsonism.

During hospitalization, additional diagnostic procedures were done. Findings of laboratory blood analysis, urine biochemical analysis, peripheral blood smear, serum iron and iron binding data [Fe – 8 μmol/L (11–31 μmol/L); unsaturated iron binding capacity (UIBC) – 32 μmol/L (35–54 μmol/L) total iron binding capacity (TIBC) – 40 μmol/L (45–80 μmol/L); ferritin – 299 μmol/L (22–561 μmol/L)] were normal, as also additional serological blood tests (for echinococcosis, cysticercosis borreliosis, plasmodium, viral hepatitis, syphilis and HIV). Lumbar puncture was done and cerebrospinal fluid analysis showed normal findings. The values of ceruloplasmin and copper in serum and urine were significantly different from the reference values: serum ceruloplasmin was markedly reduced – < 0.077 g/L (reference values: 0.2–0.6 g/L); copper concentrations were significantly decreased 3.77 mmol/L (11.90–20.41 mmol/L) as 24-hour urine copper < 0.01 mg/24 h (reference value < 0.05 mg/24 h). Control EEG was normal. When auditory brainstem evoked potentials (AEPMS) was done, bilateral dysfunction at the level of the rostral part of the brainstem was found. The finding of visual evoked potential (VEP) was normal. CT scan showed secondary deposits of metal in basal ganglia. Endocranium MRI showed atrophic changes in the brain parenchyma with a metal deposition in the nucleus *lentiformis* and *pars compacta* of the substantia nigra (Figure 1).

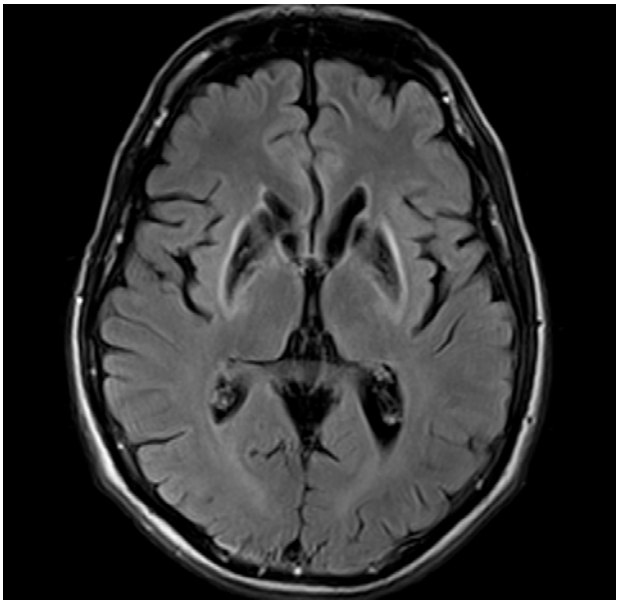

Fig. 1 – Magnetic resonance imaging of the endocranium shows atrophic changes in the brain parenchyma with deposition of metal in the nucleus *lentiformis* and *pars compacta* of *substantia nigra.*

Transcranial Doppler (TCD) discovered a decreased flow. Multislice computerized tomography (MSCT) of the liver was normal: homogenous structure without focal changes. The possibility of liver biopsy was considered, but it was not approved by the patient. Ophthalmological examination was performed in the first week after admission, then a month later and in both cases the results were normal. Control ophthalmological examination 3 months after admission to the hospital, demonstrated for the first time the occurrence of Kayser-Fleischer's rings.

Regardless of the lack of confirmation of the existence of Wilson's disease 4 weeks after admission to the hospital, penicillamine therapy was administered with concomitant symptomatic polyvitamin and sedative therapy. Regular monitoring of urine copper concentration showed a significantly positive response to the therapy, which resulted in increased excretion of copper in urine (400 times). The definitive diagnosis of Wilson's disease was established 3 months later, after receiving the results of molecular genetic analysis. Genetic testing which was conducted in 2 independent laboratories confirmed heterozygous carrier of mutations for Wilson's disease: in exon 8 (229 Ins C and c.236G-A) and small insertion in exon 8 (c.insC2304-2305), as also in exon 16 (A 1140 V).

Discussion

The presented case of Wilson's disease has several specific features that distinguish it from most other patients with the same diagnosis. The first peculiarity consists primarily of the dominant clinical psychiatric disorder, and because of that, the patient was diagnosed with a psychotic disorder, and for nearly 6 months was treated accordingly, with antipsychotic therapy, and during that period he manifested theraporesistance. Similar cases were described elsewhere [18, 19].

With psychopathological phenomena manifested on admission which had a character of non-specific psychotic disorder, neurological signs which were also observed, and with anamnestic data about recent return from Africa, where he had a brief episode of high fever, all pointed to a possible infectious etiology.

After a detailed laboratory analysis of blood and cerebrospinal fluid, when infectious disease of CNS was excluded, and when neuroradiological imaging demonstrated the presence of metal deposits in brain structures, several differential diagnosis resolution were discussed: panthotenate kinase-associated neurodegeneration (PKAN) formerly called Hallevorden Spatz syndrome, Wilson's disease and aceruloplasminemia. Neuroimaging indicated the existence of metal deposits in specific CNS structures which was not enough to resolve the differential diagnosis between these diseases. Similarities in clinical presentation – the presence of neurological and psychiatric symptoms, characteristic for all these disorders did not contribute to further precise diagnosis. More detailed diagnostic determination was achieved with laboratory analysis of blood and urine: normal values o f laboratory analysis of iron excluded diagnosis of PKAN. The absence of signs of diabetes mellitus, anemia, and retinal degeneration, with normal iron and ferritin concentrations excluded the diagnosis of aceruloplasminemia [20]. At the same time, significantly lower levels of ceruloplasmin and copper in serum indicated the presence of Wilson's disease, despite the absence of pathognomonic signs: Kayser-Fleischer rings, metal deposits in liver and decreased values of copper in urine [12].

After clinical decision to initiate penicillamine therapy, which led to the improvement of mental and general health of the patient, the diagnosis of Wilson's disease was obtained

ex-iuvantibus [21]. No sooner than 2 months after the beggining of treatment, ophthalmological examination showed Kayser-Fleisher rings, and 3 months later, the results of molecular genetic analysis confirmed the diagnosis of Wilson's disease [22].

Conclusion

Atypical form of Wilson's disease can remain undetected for a long time if it is masked by dominant or exclusive psychiatric symptoms. If clear clinical signs and symptoms (neurological, ophthalmological) are not fully present, and unambiguous laboratory findings (decreased concentrations of copper and ceruloplasmin in serum and increased concentration of copper in urine), it is necessary to perform molecular genetic analysis in order to confirm the definitive diagnosis.

Early diagnosis and effective treatment improve the outlook. The prognosis of Wilson's disease is excellent provided that the treatment starts before irreversible damage.

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