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Psychiatric disturbances as a first clinical symptom of Wilson's disease – case report

Tomasz Litwin[1], Karolina Dzieżyc[1], Michał Karliński[1], Tomasz Szafrański[2], Anna Członkowska[1,3]

[1] Second Department of Neurology, Institute Psychiatry and Neurology in Warsaw
[2] Specialist Medical Practice Tomasz Szafrański, Warsaw
[3] Department of Experimental and Clinical Pharmacology, Medical University of Warsaw

Summary

Introduction. Wilson's disease (WD) is an inherited disorder of copper metabolism with wide spectrum of clinical symptoms, mainly hepatic or neurological. Psychiatric disorders occur less frequently and are not pathognomonic for WD. However, in almost 20% of cases they are in fact the first clinical manifestation of WD.

Aim. The aim of this paper is to emphasise the importance of including WD in differential diagnosis of psychiatric disorders in young adults, as well as caution in initiating psychiatric treatment for patients with already established diagnosis of WD.

Methods. Case report of a patient with primarily psychiatric manifestation of WD.

Results. The authors present the case of a 26-year-old patient treated for 3 years due to depressive syndrome who was diagnosed as WD in the differential diagnosis shortly after extrapyramidal symptoms developed. During the further WD treatment the manic episode occurred. The patient was treated with atypical neuroleptics and anxiolytics, with good psychiatric effect, but with severe neurological deterioration. However, long term use of valproic acid and olanzapine combined with continuation of anti-copper treatment and rehabilitation resulted in good psychiatric and neurological outcome.

Conclusions. WD should be always considered in differential diagnosis of psychiatric disorders in young patients, especially if they present additional extrapyramidal or hepatic symptoms. It is also extremely important to remain cautious when drugs with high affinity to dopamine D2 receptors need to be initiated in patients already diagnosed with WD, as they may result in severe and often irreversible neurological complications.

Key words: Wilson's disease, bipolar disorder, basal ganglia disorders

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Introduction

Wilson's disease (WD) is an inherited autosomal disorder of copper metabolism disturbances that cause pathological accumulation of copper in different organs and tissues (mainly liver, brain, cornea, kidneys) leading to their symptomatic damage [1, 2].

As multiple organs may be affected, the disease varies in terms of initial symptomatology and the age of their onset (from 3 year-olds in case of hepatic symptoms, up to 8th decade for neurological manifestation) [2]. Clinical symptoms of WD are usually developed between 2nd and 3rd decade of life. They result from injury of: 1) liver (from asymptomatic hypertransaminasemia, hepatitis and cirrhosis, up to fulminant liver failure); 2) central nervous system (different extrapyramidal and psychiatric symptoms); 3) other organs, especially eyes (Kayser-Fleischer ring, sunflower cataract), skeletal system, kidneys.

Psychiatric disorders in WD are not specific and involve a wide range of symptoms. In childhood these are mainly personality disturbances, impulsiveness, affective and behavioural disorders. Adult patients usually develop behavioural disorders, affective disorders (depression or bipolar disorder), psychotic schizophrenia-like symptoms or cognitive disturbances [2].

Noteworthy, psychiatric disorders may develop in course of disease but also present as initial symptoms of WD [3–7]. Therefore, WD needs to be included in the differential diagnosis of psychiatric disturbances, especially if they coexist with liver injury or abovementioned neurological signs. One should also account for the family history of hepatic and neurological symptoms, especially of unknown aetiology.

On the other hand, development of psychiatric features in a patient previously diagnosed with WD pose a major therapeutic problem due to possible drug-associated adverse events. Psychiatric drugs that modulate dopaminergic pathways (e.g. neuroleptics or anti-depressants) may exacerbate or even cause neurological symptoms [8–11]. Therefore, close cooperation between psychiatrists and neurologists is necessary.

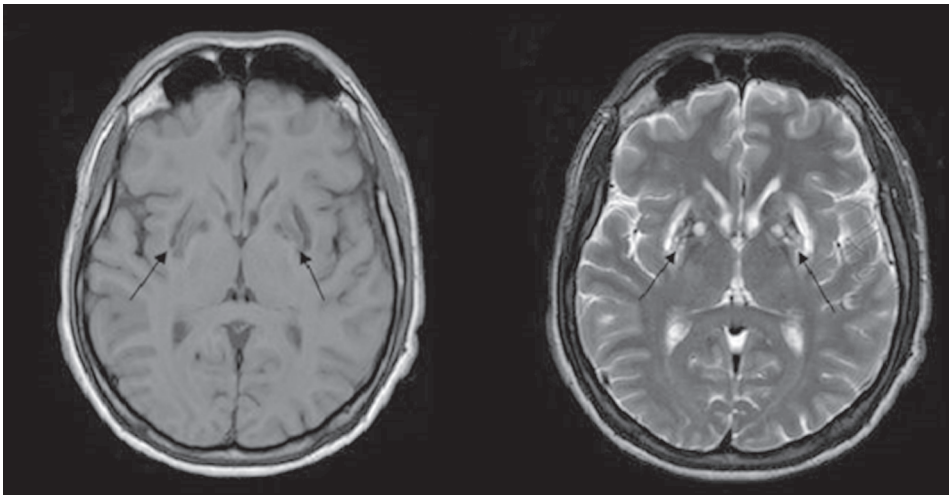
Aim

Our aim was to emphasise the importance of including WD in the differential diagnosis of young adult who develop psychiatric disorders and have concomitant extrapyramidal and/or hepatic symptoms. Additionally, we discuss the problem of psychiatric pharmacotherapy in patients already diagnosed with WD.

Case report

A 26-year old male with no past medical history in September 2010 became depressive, and started to complain of problems with concentration, headache and sleep

disturbances. The patient initially reported to a neurologist who referred the patient to a psychiatrist. He was diagnosed with depression and received clomipramine (75 mg) combined with mianserin (5 mg) with little effect. His first neurological symptoms occurred in August 2012. They included slight dysarthria, sialorrhoea and postural tremor of the right upper limb. Magnetic resonance (MR) of the brain revealed symmetric changes in putamen and globi pallidi hyperintense on T2-weighted images and hypointense on T1 images (Figure 1), which were suggestive of WD.



A B

Figure 1. **The brain MRI of patient with WD: A) decreased signal intensity on T1 weighted images in both putamen and globi pallidi (black arrows); B) increased signal intensity on T2 weighted images in both putamen and globi pallidi (black arrows)**

The diagnosis was made in March 2013 in our centre. It was based on clinical presentation (neuropsychiatric signs and symptoms; hepatic involvement: bilirubin 1.7 mg/dl with the normal range 0–1.2; presence of Kayser-Fleischer ring) and copper metabolism. There was a decrease in serum ceruloplasmin concentration (2.1 mg/dl; normal range 25–45) and total serum copper concentration (36 μg/dl; normal range 70–140), whilst urinary copper excretion was increased (91 μg/24h; normal range 0–50). WD was further confirmed by genetic testing (p.H1069Q mutation in both alleles of *ATP7B* gene). Anti-copper treatment was initiated (180 mg of elementary Zn2+/24h), clomipramine was ceased and mianserin was maintained at a lower dose (5 mg/night) because of persisting problems with falling asleep.

Postural tremor resolved completely, speech disturbances became less pronounced and the patient was able to continue his occupation as a manual worker. However, in the middle of the June 2013, there was a sudden psychiatric deterioration manifested as mania with active aggression towards other people. The patient was described as nervous, agitated, vulgar, aggressive, having racing thoughts with normal orientation. He required involuntary admission to a psychiatric ward and needed to be restrained in a straightjacket. After the diagnosis of manic episode was established, the patient received quetiapine and aripiprazole with no satisfactory response. He was subsequently switched to olanzapine (15 mg/24h) and valproic acid (1500 mg/24h) with ad hoc doses of clorazepate and hydroxyzine achieving gradual psychiatric improvement. However, within the first 2 weeks of hospital stay he developed progressive speech disturbances and severe problems with swallowing that required nasogastric feeding tube.

At that point, the patient was transferred to our department for further neurological treatment. On admission he showed anarthria, severe dysphagia, sialorrhoea, orofacial dyskinesias and slight postural tremor of upper extremities. Copper metabolism tests indicated that the treatment of WD was proceeding correctly. Serum concentration of zinc was high (220 μg/dl) and calculated free copper concentration (7.2 μg/dl) was within range in proper treated patients (5–15 μg/dl). Treatment with valproic acid and olanzapine was continued (1500 mg and 15 mg, respectively). During 2 months of speech therapy dysarthria and dysphagia resolved completely. However, orofacial dyskinesias and slight postural tremor of upper extremities persisted. After discharge from the hospital, olanzapine was gradually discontinued and well tolerated normothymic treatment with valproic acid was continued.

Discussion

Physicians who have no everyday experience in managing WD tend to believed that clinical manifestation of hepatolenticular degeneration is caused only by liver injury (hepatic failure) or subcortical brain lesions (extrapyramidal symptoms).

However, psychiatric features of WD were even described by S.A.K. Wilson in his seminal monograph from 1912. Disturbances described as “emotionality” and “mental abnormalities” were recognised in 8 of 12 (66%) cases of hepatolenticular degeneration (later named Wilson’s disease) [1]. Even more, in 6 patients personally examined by S.A.K Wilson initial symptoms of WD included emotional lability (2 patients) and “schizophrenia-like” disorder (2 other patients) [1].

According to the literature, psychiatric disorders are developed by 50–70% of patients and in 20% they may be the first manifestation of WD [2, 3–7, 12–15]. Akil et al. distinguished five categories of psychiatric symptoms in this group of patients:

1) cognitive impairment (< 25%); 2) personality disturbances (46–71%); 3) affective disorders (30–60%); 4) psychosis (< 8% of patients with neurological symptoms); 5) other rare disturbances (e.g. anxiety or anorexia) [12].

It is possible that clinical presentation of WD involves psychiatric symptoms alone. Therefore, it needs to be included in differential diagnosis of psychiatric disorders, especially in young patients (2nd–3rd decade of life) [2, 16]. In the literature there are reports of using routine serum ceruloplasmin assays as a screening tool for WD (decreased level) among patients with psychiatric disturbances of unknown aetiology. Unfortunately, the sensitivity turned out to be unsatisfactory [17]. It has been proposed to combine basic liver tests (of course before introducing psychiatric drugs), ophthalmologic examination for Kayser-Fleischer ring, neuroimaging (magnetic resonance of the brain may be suggestive of WD) and taking careful family history of hepatic and neurological disorders [16]. In case of revealed abnormalities, they should be followed by detailed diagnostic workup according to EASL guidelines [2].

WD is a degenerative disorder that responds to treatment. However, the outcome depends on the time to treatment initiation, meaning time from the onset of symptoms to the final diagnosis [18]. Unfortunately, this delay is the longest among patients with psychiatric presentation (mean 2.4 years, compared to 0.5 years for hepatic presentation and 1.5 year for neurological presentation) [2, 16].

Psychiatric symptoms of WD cause considerable diagnostic and therapeutic problems.

Possible side effects of neuroleptics and anti-depressive drugs that modulate or disrupt dopaminergic system make psychiatric treatment in WD extremely difficult [8]. WD pathology involves extrapyramidal system. Patients, especially young males, are at increased risk of developing classical medication induced movement disorders (MIMD) [8, 10]. However, neurological deterioration observed after introduction of anti-dopaminergic drugs often manifests as exacerbation of preexisting symptoms and it cannot be labelled as classical MIMD, which was also the case in reported patient [10]. There are a few case reports of effective quetiapine, clozapine, olanzapine and lit salts use [2, 19–21]. However, there are also reports of dramatic neurological deterioration after initiation of neuroleptics [9, 11].

Studies of mortality and worsening in WD suggest that psychiatric symptoms and their treatment may increase the risk of poor outcome [9]. Unfortunately, recommendations of European Association for the Study of the Liver (EASL) and American Association Study of The Liver Disease (AASLD) provide no guidance on how to manage psychiatric disorders in WD [2]. It has been only emphasised, that all agents potentially affecting central nervous system should be initiated very carefully [2, 9, 22].

WD patients appear to be extremely susceptible to adverse effects of dopamine antagonists (neuroleptics, anti-depressants or even anti-emetics) [8–10]. Decreased

number of dopaminergic D2 receptors in subcortical nuclei of the brain lowers threshold for drug-induced movement disorders. The risk of complications is considered to be higher if the typical antipsychotics are used. However, in presented case progressive neurological deterioration occurred after initiation of atypical neuroleptics (aripiprazole or quetiapine). In WD patients with bipolar disorder lit salts have been described as effective and safe. Lit salts are supposed to have less influence on dopaminergic transmission, they are not metabolised in liver are unlikely to cause leucopoenia (as opposed to clozapine) [19]. Some even speculate that lit salts may modulate P-type sodium-potassium ATPase involved in copper transport and WD itself. However, those hypotheses need to be verified in further studies [19, 23, 24].

Conclusions

In is necessary to considering Wilson's disease in the differential diagnosis of psychiatric disorders in young adults, as even up to 20% of WD starts with psychiatric symptoms [2–7]. Coincidence of neurological symptoms (mainly extrapyramidal) and liver disease should be a red flag indicating that primarily psychiatric patient may in fact suffer from WD [2]. Noteworthy, typical brain lesions on MR and Kayser-Fleischer ring can be found in > 90% of WD patients with neuropsychiatric presentation [2]. It is also extremely important to consider potential adverse effects of psychiatric drugs in patients already diagnosed with WD and avoid drugs that may cause extrapyramidal symptoms [9]. It refers also to patients who had subclinical course of disease.

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Address: Tomasz Litwin
Second Department of Neurology
Institute Psychiatry and Neurology
02-957 Warszawa, Sobieskiego Street 9