CASE REPORT

Insomnia as a Rare Neuropsychiatric Presentation of Wilson Disease

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Abstract

Objective: Wilson’s disease (WD) is a rare disorder of copper metabolism with hepatic, neurological and psychiatric manifestations. This case describes insomnia as a rare primary psychiatric presentation of WD. Methods: An 18 year old gentleman presented with three months of poor sleep. There was no depressive, manic, psychotic, anxiety or cognitive symptoms. He was diagnosed with WD three months ago. Physical examination was normal however Kayser-Fleischer rings were noted. MRI brain demonstrated symmetrical signal abnormalities noted in the head of the caudate nucleus, putamen and globus pallidus. His insomnia worsened on increased dose of chelating agent so the agent was reduced. Longitudinally he developed depressive symptoms so has been commenced on mirtazapine. Discussion: Psychiatric complications of WD are found in initial presentation in 30-67\% cases. Underlying scientific mechanisms proposed include brain copper toxicity, presynaptic SERT availability, and alternative metabolic influences. Treatment focuses on chelating agents and psychotropic augmentation.

Keywords: Wilson’s Disease, Insomnia, Psychiatry

Introduction

Wilson’s disease (WD) is a rare autosomal recessive disorder of copper metabolism\textsuperscript{1,2}. A defect of gene ATP7B causes copper accumulation primarily in the liver and brain, secondary to reduced biliary excretion of copper. This has hepatic, neurological and psychiatric sequelae\textsuperscript{3}. Dening’s seminal review suggested the main psychiatric symptoms were depression (30\%), incongruous behavior (30\%) and cognitive impairment (28\%)\textsuperscript{4}. We examine an interesting psychiatric presentation where insomnia was the primary presenting complaint independent of any affective, psychotic or neurotic symptoms.

Case Report

This 18-year-old gentleman was initially referred with the presenting complaint of
poor sleep for three months. He had been diagnosed with WD three months prior to first contact with psychiatry and was currently being treated with penicillamine, a chelating agent. He had trouble initiating sleep, and had difficulty with sleep maintenance but did not have terminal insomnia. There were no other depressive symptoms and no suicidal ideations or thoughts of self-harm.

There were no manic or anxiety symptoms. No obsessions or compulsions were evident. Other than his newly diagnosed WD, there were no new emotional stressors in his life.

His responses were slower and occasionally he was unable to remember things he had done. However, gross cognitive abilities remained intact upon testing orientation, attention, concentration, and recent and remote memory. He developed dysarthria but was able to communicate via texting. His premorbid ability to solve complicated mathematical problems remained intact. He had subsequently and rather rapidly developed dystonia and dysphagia whilst on chelating agents.

There were no other previous medical, surgical and psychiatric history, and no family history of psychiatric illness. However, there were two young deaths of unknown aetiology at age 40 and 17 respectively associated with progressive neurological deterioration. Otherwise, birth and developmental history were uneventful and he completed secondary school with good academic performance. There is no history of smoking, alcohol or substance use.

He first presented to the medical team in November 2015 with gastrointestinal symptoms (retching and vomiting) and neurological symptoms (twitching, drooling, pronounced tremor). On examination he was not jaundiced and there was no hepatosplenomegaly or ascites. There was tongue fasciculation, dysarthria and cogwheel rigidity. Pupils were equal and reactive but Kayser-Fleischer rings were noted. Upper and lower limb neurological examinations were grossly normal and there were no cerebellar signs. His gait demonstrated reduced arm swing with no broad base.

Liver function tests were grossly deranged, prompting an ultrasound abdomen which indicated a coarse liver and thickened gallbladder. MRCP liver showed cirrhosis with multiple nodules. MRI brain demonstrated symmetrical signal abnormalities in the head of the caudate nucleus, putamen and globus pallidus, suggestive of Wilson's disease. Ophthalmological examination confirmed the presence of Kayser-Fleischer rings.

His Leipzig Score is 5 (KF rings present - 2, neurological symptoms - 1, ceruloplasmin 0.09 g/L – 2), establishing his diagnosis based on Leipzig criteria. There is no family history of hepatocellular carcinoma. Otherwise liver function tests are less than 1.5 times the upper limit of normal. The AntiHAV total is reactive but there is no AntiHBs or AntiHCV. AMA, ANA, anti-gastric parietal cell antibodies, ANCA, and anti-SMA are all negative.

He was started on Penicillamine 500 mg bd, Zinc Acetate 50 mg tds and Pyridoxine 30 mg daily on 12.2.16. The psychiatry team initiated as-required T. clonazepam 2mg. After his penicillamine was increased to 500 mg tds, his sleep worsened and he became increasingly restless at night. This was alleviated by regular dosing of clonazepam. His penicillamine was also reduced to 250 mg tds.
However, over the months he has become more anhedonic with depressed mood, occasional crying, hopelessness, and worsening of insomnia upon follow-up. Though not meeting criteria for a major depressive episode, mirtazapine was commenced as the mood symptoms were deemed sufficiently severe. The dysphagia worsened, requiring nasogastric tube feeding, and he is gradually becoming less ADL independent. We have advised the parents for support group and counselling as well as screening of immediate family members for WD.

**Discussion**

WD proper and its treatment\(^5\)\(^6\) can cause psychiatric manifestations, found at initial presentation in 30-64% of cases\(^4\)\(^7\). Psychiatric symptoms are correlated with poorer prognosis\(^8\) and less favourable outcome following liver transplantation\(^9\). However ambiguity remains if this is secondary to psychiatric symptoms or due to brain damage following copper accumulation.

Cognitive impairment diminished over time and was present in only 5% of patients assessed at the second follow-up. Neurologic manifestations at initial presentation range between 18-68%\(^10\)\(^12\), classified into dysarthric, dystonic, tremor, pseudosclerotic or parkinsonian types\(^13\).

Insomnia is a recognised neuropsychiatric presentation of WD\(^14\)\(^15\). It however is usually part of an affective disorder presentation\(^16\)\(^17\). In this case report, the presenting complaint is insomnia independent of affective symptoms.

Early researchers postulated that psychiatric symptoms indicated advanced disease, copper toxicity leading to irreversible brain damage, or were secondary to liver malfunction eg. hyperammonaemia linked to hepatic encephalopathy\(^18\). No demonstrated relationship exists between copper levels and symptomatology levels\(^4\). However, availability of presynaptic SERT in the hypothalamus of depressed WD patients correlated negatively with the individual severity of the depression\(^19\)\(^20\).

No neuroimaging studies so far have discovered correlations with psychiatric presentations in WD\(^3\). Diffuse but uneven electroencephalographic (EEG) topographic abnormalities in WD patients were noted\(^21\)\(^22\).

Treatment is two-pronged – treating the primary illness with chelating agents, and also augmentation with psychiatric medications. However, WD causes a higher propensity of extra-pyramidal side effects (EPSE) and neuroleptic malignant syndrome\(^23\). Unfortunately, taking into account the hepatic dysfunction of WD, nearly all psychiatric medications are hepatically metabolized. As such the roles of lithium (which has zero hepatic metabolism)\(^24\), electroconvulsive therapy\(^25\), and psychological therapies like cognitive behavioural therapy\(^26\) have demonstrated efficacy.

**Conclusion**

WD, though rare, is certainly a common confounder. The index of suspicion should be raised in a first presentation with no family history of mental illness, who has neurological signs or any family history of neurological illness or early death. Psychiatric symptoms cause a significant proportion of morbidity in the illness course and should be treated accordingly.
Disclosure

Conflict of interest: None.

References


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