CASE REPORT

Psychiatric Presentation in Wilson disease – Report of Two Cases

Nazariah Aiza H¹, Aisah AR¹, Anita C¹, Yeoh SH³, Ng CG¹²

¹Department of Psychological Medicine, University Malaya Medical Centre
²Psychological Medicine Research Group of University Malaya (PARADIGM)
³Department of Psychiatry, Hospital Universiti Kebangsaan Malaysia

Abstract

Wilson disease is an inherited metabolic disorder. It is an autosomal recessive disorder caused by mutation of ATP7B gene, which results in excessive accumulation of copper in the body and deposition in various organs. The clinical presentation varies and neuropsychiatric manifestations are common. It is a diagnostic challenge in the initial phase where it mimics other psychiatric conditions and the diagnosis of Wilson disease is based on a combination of laboratory tests and clinical features. Wilson disease treatment comprises of copper chelating therapy such as D-Penicillamine and zinc sulphate whereas the behavior and mood symptoms response well with atypical antipsychotic treatment. The present report illustrates two cases of Wilson disease in middle-aged patients. The first presentation involved changes in behavior and personality. There was some delay in making the diagnosis in the initial stage. Both cases were diagnosed to have Wilson disease after further investigations. Their condition improved with the combination of copper chelating agent and atypical antipsychotic. In conclusion, it emphasizes the awareness of psychiatric manifestations as the initial presentation of Wilson disease.

Keywords: Wilson disease, Psychiatric manifestation, Atypical antipsychotic, Chelating therapy

Introduction

Wilson disease, otherwise known as progressive hepatolenticular degeneration, is a rare autosomal recessive disorder caused by the mutation of ATP7B gene. ATP7B gene is responsible for the formation of copper transporting P type ATPase (Wilson disease protein). As a result, the transportation of copper in the body is impaired in Wilson disease. This copper is then deposited in various organs where it causes dysfunction of that particular organ such as liver, brain and kidney¹.

The clinical presentations of Wilson disease are broad and involve multiple organs. It is usually asymptomatic in early life period and then presented with unexplained liver, neurological or psychiatric problems².
Hepatic manifestation usually appears earlier (between 8 to 18 years old) than the neurological manifestation (in early adulthood). Liver disease ranges from asymptomatic form with elevated liver enzymes or liver enlargement, chronic hepatitis with steatosis, and fibrosis to liver cirrhosis or chronic liver failure. Neurological disorders occur in 40-50% of patients with Wilson disease. It is characterized by cumulative motor dysfunction. Clinical signs include asymmetrical distal accentuated tremor of the hands, wing beating tremor and tremor of the head, rigidity, dystonia and bradykinesia. The mean age of onset of psychiatric manifestation in Wilson disease is around 20 years old. It could be classified as affective disorder spectrum and schizophreniform-illness. The commonest psychiatric symptoms include incongruous behavior, irritability, depression, and cognitive impairment. There has been a reported case of Wilson Disease presenting with non-persecutory delusional disorder and alcohol abuse in the absence of neurological signs.

The diagnosis of Wilson disease is based on a combination of laboratory tests and clinical features. The commonly used laboratory tests are 24 hour urinary copper excretion, hepatic copper concentration, serum free copper and ceruloplasmin concentration. The presence of Kayser Fleischer rings during ophthalmological examination is not a specific but an important sign for Wilson disease. It indicates that free copper has been released into the circulation. Given the variability of the biochemical and clinical features of Wilson disease, mutations analysis is becoming more and more essential to confirm a suspicion of the disorder.

The treatment of Wilson disease is decoppering therapy. It is to reduce the copper accumulation in the body, either by enhancing its urinary excretion or by reducing its intestinal absorption. D-Penicillamine is used to enhance urinary excretion of copper by forming copper-penicillamine complexes. The complexes are then excreted in the urine. Treatment usually starts at lower doses and increases gradually. Pyridoxine (vitamin B6) is given as adjuvant therapy to prevent vitamin B6 deficiency. Some patients were found to be intolerant in the initial period due to side effect or hypersensitivity and became tolerated to the treatment eventually.

Another treatment option is zinc sulphate. Zinc increases the levels of intestinal cell metallothionein which has a strong affinity for copper. This inhibits further copper absorption and promotes its loss in the faeces. It is mainly used for asymptomatic patients or maintenance therapy. Zinc sulphate was found to cause less neuropsychiatric complication as compared to D-Penicillamine. Liver transplantation is the ultimate treatment for patients with Wilson disease. However, neuropsychiatric symptoms are always a contraindication for liver transplantation.

**CASE REPORT 1**

A 49 year old Chinese, lady, housewife, married with 2 children presented to us with abnormal behavior for the past 6 months. Her illness started with tremors of both her hands and caused impairment in her daily function. The tremors were non-remitting, but lesser when she was asleep, according to her husband. The symptom went on for a few months and she began to have occasional jerky movement of her head. This led her feeling awkward in social gatherings and she started to avoid going out. She was seen by a general practitioner
who subsequently referred her to a private psychiatrist. The psychiatrist treated her with oral Sertraline and Alprazolam for anxiety. The tremors did not improve, and her jerky head movements were more frequent.

One week prior to consultation in our centre, her condition deteriorated whereby she behaved abnormally. She did not sleep at night and like to wonder outside her house. She would order food at the restaurant without paying. She talked and asked for money from strangers. She claimed to be the owner for all shops and restaurants in her area where she started to eat and take things from shops without making any payments. She occasionally laughed and talked very loudly to her sister. Her speech was irrelevant and incoherent most of the time. She also spent excessively on lottery and need to be coaxed to have her bath and change her clothes. She would turn on the television and radio loudly at home causing a lot of disturbance to the neighbors. She became very argumentative with her mother and her family found it difficult to talk to her as she was talking fast and difficult to be interrupted.

On the day of consultation, the patient appeared very agitated and assaultive toward her sister. She was found to have no history of auditory hallucination, deliberate self harm or illicit substance use. Upon further enquiry, the patient’s 45 year old brother was diagnosed with Wilson’s disease about 10 years ago and is still under treatment.

Physical examination revealed that she had involuntary jerky rhythmic movement of her head – titubation which persisted even with distraction. She also had involuntary resting tremors of both her upper limb. Her gait was fairly normal. There was no past-pointing or dysdiadochokinesia. Motor examination was normal and her sensation was intact. She had Kayser Fleisher rings under slit-lamp examination.

Blood investigations showed that complete blood count, liver function test, renal function test, random blood sugar and serum magnesium were all within normal limits. The serum ceruloplasmin were <0.09 (Low) and serum copper were 5.1 (Low). The urine copper 24 Hours were 0.78 (High). The CT and MRI brain reported as normal study. No cerebral atrophy seen and basal ganglia was normal.

She was diagnosed to have Wilson disease and started on D-Penicillamine 250mg bd (copper chelation therapy) by the neurologist. She and her husband were counseled about the disease and life-long therapy. She was also seen by the psychiatrist and diagnosed as having psychosis secondary to Wilson disease according to DSMIV. She was started on tablet Olanzepine 2.5 mg BD. Her psychotic symptoms resolved with the medication and the patient was much better and manageable. However, her tremors were still present. She was on the atypical antipsychotic treatment for a year at the time this case was reported. There was no report of any adverse event.

CASE REPORT 2

A 35 year old Malay gentleman who is a lecturer of civil engineering in a local university was presented to us with the changed of behavior for the past two months. According to his wife, he was noticed to be easily irritable and increase in sexual libido. He was withdrawn and agitated where he became verbally abusive towards his parents. He also behaved disinhibited in front of his children occasionally. A week prior to admission, he checked into a luxury hotel alone for no
specific reason. He was behaving aggressively in a hotel whereby he shouted at hotel staff and damaged hotel property. As a result, he was arrested and sent for assessment in a government hospital. He was admitted for five days and no conclusive clinical impression was made. He was then discharged with no medication and to be seen again in outpatient clinic. His condition did not improve and became more restless at home. As a result, he was brought by family to our centre for consultation. He has no past history of mental illness and neither did his family. There is no history of illicit substance use.

Physical and neurological examination showed that he had right wrist cogwheeling, Left hand passpointing, bradykinesia, difficulty using small muscles of the hands and apraxia. He had difficulty initiating gait and had shuffling gait upon mobilizing. He had loss of arm swing when walking. He had Kayser Fleisher rings and it was confirmed by slit-lamp examination. On mental state examination, he was forthcoming however easily irritable and provocative. His speech was coherent and relevant but monotonous. There was increase in ideas and he was paranoid towards his wife. At some point during admission he had tactile hallucination saying he was bleeding from his nose, rectum and ears.

Mini mental State examination showed he had micrographia and impaired cognitive function whereby he scored 22/30. There was impairment in area of recall, orientation and unable to follow complex commands.

Blood investigations revealed that complete blood count, renal function test, thyroid function test, random blood sugar and serum magnesium were all within normal limits. Screening for hepatitis, HIV and VDRL were all negative. Liver function test (LFT) showed elevated GGT 170 and low total protein and albumin count, 62 and 30 respectively. The serum ceruloplasmin were <0.07 (Low), serum copper were low and the 24 hours urine copper were raised. Urine porphyrin was negative. Both CT and MRI brain showed cerebral and cerebellar atrophy with no intracranial bleed. The atrophy was more prominent in the frontal lobe.

He was diagnosed to have Wilson disease and started on D-Penicillamine 250mg bd in the neurology ward. He was also seen by the psychiatrist and treated as mood disorder due to Wilson disease according to DSM IV. He was started on quetiapine XR 100mg daily and the dose was titrated up 400mg on discharge. He became less irritable and more manageable at home. He was on atypical antipsychotic treatment for a year at the time this case was reported and did not experience any adverse events.

Discussion

Wilson disease is due to inborn error of copper metabolism and it may present in the early phase with neuropsychiatric symptoms. This is concurred with Wilson himself, whereby he described behavioral aspects of this disease in 8 of 12 of his patients and called this “psychical” form in his initial monograph6. Disease of inborn errors of metabolism with neuropsychiatric symptoms may often lead to final CNS dysfunction, delirium and coma9. The presentation for Wilson’s disease is varied and proves to be a diagnostic challenge. This is because psychiatric manifestations can present early in the disease progression and it can occur before hepatic and neurological manifestation2. The psychiatric manifestations for Wilson’s disease are divided into 5 domains: personality changes,
affective disorders, psychosis, cognitive impairment and others. The most common psychiatric manifestation is personality changes in particular irritability and aggression accounting for (45.9%) and depression followed with (27%). Among the less frequent occurrence are cognitive changes, anxiety, psychosis, and catatonia.

The similarity in these 2 cases is that both patients had change in personality, whereby they became more aggressive and impulsive. In the first case, the patient felt that she own the shops and spent excessively on lottery. There was also deterioration in function and it came to a point she was unmanageable and needed medical attention. She was treated in outpatient setting and her psychotic symptoms settled with an atypical antipsychotic, olanzapine. In the second case, the patient was disinhibited and very agitated. He was admitted and started on a different type of atypical antipsychotic, quetiapine.

Quetiapine was shown to be effective in treating affective symptoms. The dose was titrated up from 100mg to 400mg, and his mood symptoms improved. All in all, in both cases they were treated with fairly good results using atypical antipsychotic.

In conclusion, one must be aware of the possibility of an organic cause in persons who are presented with atypical psychiatric presentation for the first time. As such clinician must bear in mind that inborn errors of metabolism such as Wilson Disease can be initially presented with psychiatric symptoms.

References


**Corresponding Author**
Dr. Ng Chong Guan
Department of Psychological Medicine,
Faculty of Medicine, University Malaya,
Lembah Pantai
50603 Kuala Lumpur, Malaysia
**Tel:** +603-7949 2068  
**Fax:** +603-7955 6477

**Email:** chong_guan1975@yahoo.co.uk