Case Report

Headache as the sole manifestation of Wilson's disease

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ABSTRACT

Wilson's disease (WD) is an inborn error of copper metabolism caused by a mutation to the copper-transporting gene ATP7B. In the first decade of life, hepatic involvement predominates but neurological manifestations occur in the third or fourth decades. Studies showed Indian children with neuro WD present with behavior abnormality, speech and cognitive impairment, sub-clinical affection of visual pathway, and autonomic function. As a treatable disease, WD should be detected early in the course of the disease by any health professional at any care level, but the rare prevalence of the disease explains the lack of awareness of this disease. Even a high index of suspicion about this entity gets more difficult when the rare and atypical symptom is the only presentation of the disease. Here, we present the case of a 15-year-old girl with worsening headache for the past 3 months as the only neurological manifestation of WD, and that also without any evidence of hepatic involvement.

Key words: Copper metabolism, Headache, Wilson's disease

Wilson's disease (WD) is an autosomal recessive disorder, affecting 1 in 30,000–1 in 50,000 individuals worldwide with a genetic basis traced to the ATP-7B gene locus on the long arm of Chromosome 13 which is critical for biliary copper excretion and for copper incorporation into ceruloplasmin [1]. Absence or malfunction of the ATP7B gene which is approximately 80 Kb, consisting of 21 exons, and encoding a protein of 1465 amino acids results in decreased biliary copper excretion and diffuse accumulation of copper in the cytosol of hepatocytes [2]. With time, liver cells become overloaded and copper is redistributed to other tissues, including the brain and kidneys, causing toxicity, primarily as a potent inhibitor of enzymatic processes. The understanding and management of WD have dramatically improved since the first description of the disease by Wilson more than a century ago [3]. However, the persistent long delay between the first symptoms and diagnosis emphasizes challenges in diagnosing earlier the copper overload disorder. The most important challenge is to train physicians to recognize atypical or rare symptoms of Wilson's disease. Atypia can come from the age of onset, the liver (non-alcoholic steatohepatitis presentation), the central or peripheral nervous (neuropathy, epilepsy, and sleep disorders), or may be due to lesions of other organs (renal manifestations, osteoarticular disorders, or endocrine disturbances). Isolated biological anomalies, rare radiological findings, or inadequate interpretation of copper tests may also lead to misdiagnosis. The second challenge is to confirm the diagnosis faster and more effectively so as not to delay the initiation of treatment and expand family screening as the genetic prevalence is higher than previously expected [4].

Here, we present a case report of an adolescent girl presenting with a headache as the sole clinical presentation of Wilson's disease.

CASE REPORT

A 15-year-old girl, born to non-consanguineous parents, presented with progressively worsening headache without any systemic symptoms such as fever, vomiting, weight loss, or any other neurologic symptoms or signs for the past 3 months. She was brought to the hospital for the past 15 days, she was not even able to sleep because of the increasing severity of the headache. The headache was in the frontal area, continuous, and dull aching in nature. There was no history of slurred speech, seizures, visual disturbances, focal neurological deficit, loss of balance, confusion, memory loss, jaundice, bleeding diathesis, joint pain, or drug intake. She got many non-steroidal anti-inflammatory drugs for her complaint which gave her momentary relief only.

Her developmental milestones were normal. On examination, her vitals were stable. The liver was not palpable. The ophthalmoscopic

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examination was done for chronic headaches which revealed normal fundus, but Kayser–Fleischer rings were found in both eyes as shown in Fig. 1. Neurological examination was within normal limits.

Blood investigations revealed hemoglobin 10.3 gm/dL, WBC count-8500/mL (neutrophils-63% and lymphocytes-37%), and platelet-1.78 lakhs/mL. Liver function tests were normal, with aspartate aminotransferase of 39 and alanine transaminase of 15. Total bilirubin was 0.3, prothrombin time was 11.9, and the international normalized ratio was 1.03. Serum ceruloplasmin levels were <7 mg/dL. With the clinical diagnosis of WD, a magnetic resonance imaging (MRI) study of the brain was done to know the extent of involvement, which showed T2/FLAIR hyperintense signal in the bilateral corpus striatum, bilateral anterolateral thalami, midbrain, and the left parietal lobe as shown in Fig. 2. The patient was diagnosed with Wilson's disease and started on D-Penicillamine and zinc therapy.

After starting the patient on drug therapy, the headache subsided within 15 days and there was no worsening of neurological symptoms after starting chelation with D-Penicillamine as reported in other studies.

DISCUSSION

The clinical presentation of Wilson's disease is mostly hepatic and neuro-ocular, ranging from asymptomatic to a fulminant variety with hepatitis, portal hypertension, and diverse neurological, as well as, psychiatric symptoms. Mostly, the presentation of Wilson's disease occurs between 5 and 50 years [4]. However, early childhood WD usually presents with chronic liver disease or hemolytic anemia but the neurological manifestations are rare before the age of 10 years. Girls are 3 times more likely than boys to present with acute hepatic failure. Clinically evident liver disease may precede neurologic manifestations by as much as 10 years. After 20 years of age, neurologic symptoms predominate [5]. In patients who present with neurological manifestations, the symptomatology is predominantly extrapyramidal, such as dystonia, tremors, dysphasia, dysarthria, and ataxia. The clinical presentation in our case was quite confusing in the sense that there was no other complaint except worsening headache for the past 3 months and the ophthalmologic findings of Kayser–Fleischer ring provided the initial clue to investigate this case for Wilson's disease. In the majority of cases, the neurological symptoms are usually secondary to cerebral copper deposition, which is sufficient to destroy the nerve cells [6]. The patients may present with abdominal pain, jaundice, weakness, personality changes, depression, migraine headaches, insomnia, seizure, movement disorder chorea, and hemiballismus. Around 30–50% of patients can have neuropsychiatric symptoms including asymmetrical tremors. Other symptoms may include drooling, ataxia, personality changes, mask-like facies, and clumsiness [7]. In a series of 307 patients from India, the common clinical presentations were tremors (31.6%), dysarthria (15.6%), jaundice (12.4%), abnormal gait (8.8%), abdominal distention (7.8%), musculoskeletal symptoms (5.2%), seizures (4.9%), behavioral problems (4.6%), dystonia (3.6%), clumsiness (2.6%), drooling of saliva (2.6%), generalized weakness (2.3%), decreased scholastic performance (1.9%), changed sensorium (1.3%), bleeding symptoms (1.3%), dysphagia (0.9%), chorea (0.3%), and poor vision (0.3%) [8]. However, headache was not seen as the presenting complaint in any of the previous cases. Headache, in our case, can be due to bilateral corpus striatum, bilateral anterolateral thalami, midbrain, and the left parietal lobe calcification which was seen as hyperintense signals on MRI.

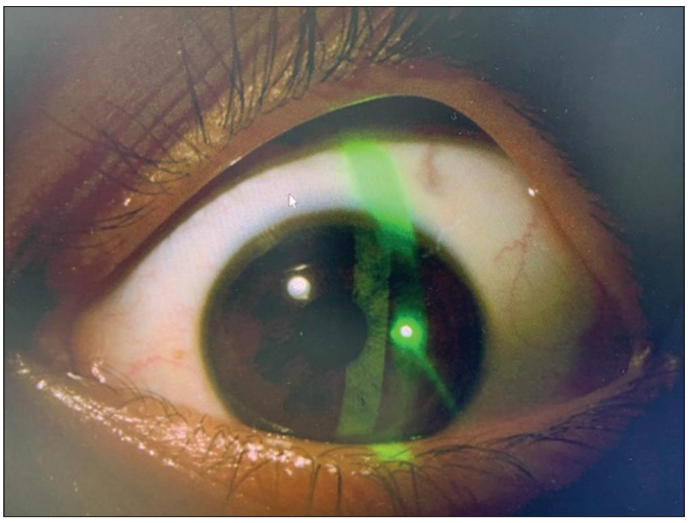

Figure 1: Kayser–Fleischer ring seen in slit lamp examination

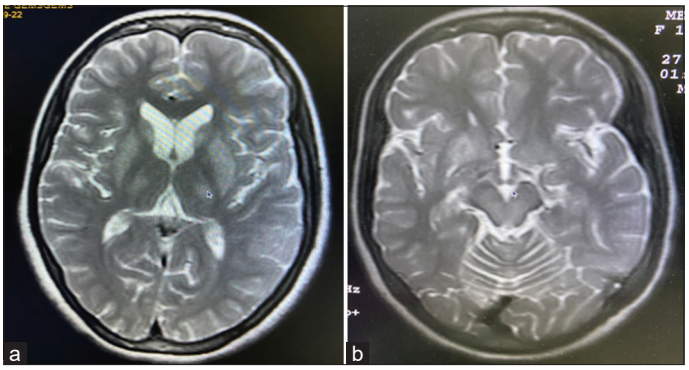

Figure 2: Magnetic resonance imaging showing (a) Hyperintensity in basal ganglia and thalami; (b) Hyperintensity in Midbrain

Studies have demonstrated MRI abnormalities to be almost universal in those with neurological disease. The MRI features included "Face of giant panda," tectal plate hyperintensity, central pontine myelinolysis-like abnormalities, and concurrent signal changes in basal ganglia, thalamus, and brainstem. These features when present are pathognomonic of WD [9]. Diagnosis is based on clinical evaluation along with biochemical and neuroimaging confirmation. Biochemical studies may show a low serum ceruloplasmin level of <20 mg/dL and increased urinary copper (100 μg copper per 24 h). Hepatic copper estimation, of more than 250 μg/g of dry tissue (Normal 15–55 μg/g) is the most definitive method of diagnosis. In our case, the diagnosis of Wilson's disease was based on the Modified Leipzig scoring system. This scoring was done on the basis of the following parameters: (1) Kayser–Fleischer ring-2 points (2) Neurological involvement-2 points (3) Decreased S. ceruloplasmin-2 points (4) typical MRI

features present-1 point. The total score in our case was 9 and according to this system, a score >4 establishes the diagnosis of WD [10].

The drug of choice in neuropsychiatric symptoms is ammonium tetra thiomolybdate which is not easily available. Our patient was put on D-penicillamine therapy along with zinc. D-penicillamine causes a negative copper balance by increasing urinary copper excretion. However, it may worsen the neurological picture in initial treatment in patients with neurological involvement. Zinc decreases the level of metallothionein in the small intestines and prevents copper from entering the circulatory system. The response to the treatment in our case was seen in the form of the disappearance of headaches. Patients are put on life-long therapy. Zinc is the choice for maintenance therapy. Patients should be monitored for ensuring compliance, the efficacy of therapy, and early recognition of side effects. Effective decoppering is assessed on 24-h urine copper and serum-free copper value [10].

WD is one of the treatable genetic disorders. Early diagnosis and institution of therapy hold the key to a good outcome. The response to therapy is dependent on various factors including compliance, duration, and severity of symptoms at the start of the therapy.

CONCLUSION

Our case had neurological involvement in the form of a headache without any other neurological or hepatic symptoms. To the best of our knowledge, a high index of suspicion of WD, in this case, was out of the question as an isolated headache presenting as the sole complaint of the disease is not mentioned in the literature. Early detection is critical as early treatment can prevent the progression of the disease.

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