CASE REPORT

Acute Encephalopathy and Refractory Hypokalemia in a 12-Year-Old Boy

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Keywords:

Wilson disease
Hepatolenticular Degeneration
Acute Febrile Encephalopathy
Kidney Tubules

Received:
17- May -2024
Accepted:
27-Jul-2024
Published:
07-Jan-2025

ABSTRACT

Wilson disease is an inherited disorder characterized by copper accumulation in various organs, leading to a wide range of clinical manifestations depending on the deposition site. Typically, symptoms of Wilson disease emerge between the ages of 5 and 35 years, primarily presenting with neurological and hepatic symptoms. This case report describes a 12-year-old boy diagnosed with Wilson disease based on low serum ceruloplasmin levels and elevated 24-hour urinary copper levels. His initial presentation included acute encephalopathy and tubulopathy with persistent hypokalemia. This case highlights the importance of a thorough evaluation, including neurological and renal assessments, to determine the underlying cause of acute encephalopathy, such as Wilson disease. Furthermore, this case shows that Wilson disease can manifest with neurological and kidney presentations despite a normal hepatic evaluation.

Introduction

Wilson disease is an inherited disorder caused by a genetic mutation in the ATP7B gene. The clinical prevalence of Wilson disease is low, estimated to range between 1.2 and 2.0 cases per 100,000 people in European countries [1]. This mutation disrupts copper transport in hepatocytes, accumulating copper in several organs, particularly the liver, central nervous system, urinary system, and cornea. Consequently, clinical manifestations vary based on the copper deposition site. Psychiatric manifestations often serve as the initial symptom, though diagnosis typically occurs after neurological or hepatic symptoms emerge[2]. Similar to its accumulation in the liver and brain, copper can accumulate in various organs, potentially impairing function. Consequently, additional early symptoms beyond

How to cite this article: Moosavian T, Pournasiri Z, Fatollahierad Sh. Acute Encephalopathy and Refractory Hypokalemia in a 12-Year-Old Boy. Iran J Child Neurol. 2025; 19(1): 107-112. https://doi.org/10.22037/ijcn.v19i1.45350

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hepatic involvement may manifest, such as renal complications and endocrine disturbances[1]. Renal manifestations include renal stones. In Wilson disease, tubular injury happens when copper accumulates in the mitochondria within the proximal and distal convoluted tubular epithelium. This buildup leads to cell death, manifesting as RTA [2, 3]. Due to the diverse clinical presentations of Wilson disease, diagnosis relies on a combination of clinical, biochemical, and genetic findings. However, current diagnostic tests often struggle to detect the disease promptly, particularly atypical presentations. Treatment options include chelating agents and zinc salts for managing Wilson disease [4].

The present study presents a case of Wilson disease with initial neurologic and renal involvement without hepatic symptoms.

Case presentation

A 12-year-old boy was admitted to the hospital because of an altered consciousness level following a fever and viral infection. During his physical examination upon admission, it was observed that the strength in both his upper and lower extremities was reduced. However, his vital signs were within the normal range (Temperature: 37 degrees Celsius, Blood pressure: 90/60 mmHg, Heart rate: 70/min, Respiratory rate: 24/min).

The patient was the first child of consanguineous parents. He had a 9-year-old healthy brother. He had experienced infrequent seizures for the past two years, controlled with a single antiepileptic drug, levetiracetam. Subsequently, he developed ataxia and progressive dysarthria following the seizures. He was treated with the antiepileptic drug, coenzyme Q10, biotin, vitamin B1, vitamin B2, vitamin B6, vitamin E, and folic acid with a possible diagnosis of mitochondrial disease. However, despite the treatment, the symptoms did not improve. The previous year's brain magnetic resonance imaging (MRI) showed symmetrical involvement of the basal ganglia, predominantly the putamen and caudate, on T2-weighted and FLAIR sequences, with a moderate T2 hyperintense signal in the lateral thalamus. Additionally, the brain magnetic resonance spectroscopy (MRS) was normal.

The antiepileptic drug was discontinued four days prior to admission due to fever and flu-like symptoms. Consequently, he experienced several episodes of tonic-clonic seizures during this period. In consideration of potential viral and mitochondrial causes, laboratory tests were conducted. Upon admission, lab results revealed the following: BUN 31 mg/dL, creatinine 0.8 mg/dL, sodium 133 mmol/L, potassium 2 mmol/L, calcium 9.4 mg/dL, magnesium 2.3 mg/dL, phosphorus 3.2 mg/dL, ammonia 280 micromol/L, and lactate 13 mmol/L. Although the Covid PCR test was negative, the Influenza PCR test was positive. Lactate and pyruvate levels were found to be normal.

In addition, the acid-base parameters indicated a pH of 7.43, Pco2 of 32.2 mmHg, and bicarbonate level of 21.4 mmol, suggesting no acid-base imbalance. However, due to an altered level of consciousness, a brain MRI was conducted, revealing bilateral thalamic, pons and midbrain involvement (Figure 1), leading to the diagnosis of acute necrotizing encephalopathy of childhood (ANEC). Subsequently, methylprednisolone treatment was initiated.

One day following admission, the patient developed fever, tachypnea, and brown urine, accompanied by a further decline in consciousness. Due to the loss of consciousness and the presence of fever, a lumbar puncture

was performed. The cerebrospinal fluid (CSF) analysis revealed normal findings, with negative CSF culture and normal CSF lactate levels. Additionally, blood culture results were negative. Due to decreased muscle tone and brown urine, the patient's serum creatine phosphokinase (CPK) levels were assessed, showing a notable increase from 1500 U/L to 15000 U/L. Liver enzymes were also elevated, with SGOT rising from 94 U/L to 406 U/L and SGPT from 40 U/L to 200 U/L. Additionally, LDH levels were raised to 1798 U/L. Urinalysis revealed specific gravity 1.030, pH 6, glucose 1+, ketone 1+, Blood 3+, and protein 2+. Microscopic urinalysis revealed WBCs 6-8/hpf and RBC 6-8/hpf. Dysmorphic RBCs were not seen in the urine.

The chest X-ray showed aspiration pneumonia, prompting the initiation of antibiotic therapy. Eventually, he was intubated due to respiratory distress, decreased oxygen saturation, and the progression of muscle weakness.

Electrolytes in the urine were measured due to low persistent potassium levels from the first day of admission (k: 2.8) and hypokalemia continued despite appropriate potassium replacement and polyuria. The results showed urine Cr 31, urine Ca 26, urine K 52, and urine Na 241. Additionally, a 24-hour urine sample was examined, and the results were as follows: urine volume 2600, creatinine 326, protein 546, calcium 1057, phosphorous 782, uric acid 390, sodium 473, potassium 112, and urea 5278. This study determined that the studied patient had tubulopathy, as indicated by the urine analysis findings, including glucosuria, hypercalciuria and increased fractional excretion of potassium (TTKG 3.5).

The kidneys revealed proportional dimensions according to age, with increased cortical echogenicity and decreased corticomedullary differentiation. Besides, the liver exhibited normal dimensions with increased parenchymal echogenicity and demonstrated heterogeneity, as observed on the ultrasound.

After three days, the CPK level decreased, and

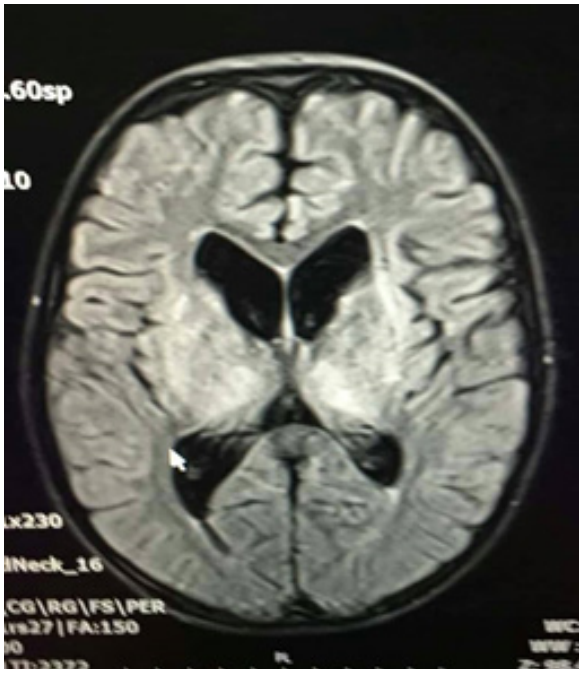

Figure 1. Bilateral thalamic necrosis accompanied by hyperintensity signals in the bilateral caudate and putamen on T2-weighted brain MRI sequencing

the patient's consciousness improved. However, extubating the patient was not feasible, not due to a decrease in the consciousness level but because of the inability to swallow saliva. Considering that consciousness does not typically improve after ANEC in mitochondrial diseases, additional investigations were undertaken to explore potential diagnosis. Given the history of dysarthria, prior symptoms of ataxia, thalamic involvement in the brain MRI, and tubulopathy, Wilson disease was also considered, prompting further evaluation.

Coombs direct and Coombs indirect were negative. Gamma GT 65, Copper serum 25 (70-150), Ceruloplasmin 6 mg/dl (20-60), Alpha 1 antitrypsin 336 (90-200), and a 24-hour urine copper test were conducted. The 24-hour urine copper was reported as 120 micrograms/dL. Consequently, the diagnosis of Wilson disease was made for the patient because of low serum ceruloplasmin levels and elevated 24-hour urinary copper levels, and d-Penicillamine was then started.

Despite the initiation of suitable therapy for Wilson disease, he expired due to complications of intubation and ventilator-associated pneumonia.

Discussion

Clinical features associated with symptomatic Wilson disease are highly variable and often present between ages 5 and 35 years[2], with neurological symptoms being the most frequent after hepatic manifestations. Neurological symptoms typically emerge about a decade later than hepatic symptoms, with dysarthria being the most common initial neurological presentation. Subjective difficulties in concentration are frequently reported among affected individuals. Motor symptoms encompass a range of manifestations, such as coordination issues, alterations in handwriting, and speech difficulties characterized by slurred speech and drooling. In untreated cases, the condition progresses typically, leading to the emergence of more pronounced neurological abnormalities [5]. Brain MRI findings in Wilson disease reveal commonly characteristic abnormalities, notably symmetric hyperintense changes visible in T2-weighted images. These changes are observed in the basal ganglia, predominantly affecting the putamen, caudate nuclei, thalami, midbrain, and pons [6]. Furthermore, a high index of suspicion is necessary for prompt diagnosis, as the clinical presentation of Wilson disease can be non-specific and may overlap with other conditions.

Renal involvement in Wilson disease is often overlooked due to its subtle manifestations, including tubular dysfunction, acid-base disorders, and nephrolithiasis[1]. In Wilson disease, the overabundance of urinary copper excretion can directly harm tubular cells, contributing to a spectrum of renal issues, including hypercalciuria and urinary calculi. Elevated levels of calcium in the urine stem from a breakdown in the reabsorption process within the distal portion of renal tubules, as well as the release of calcium from bones. Hypercalciuria, in turn, increases the risk of developing urinary calculi. Renal tubulopathy associated with Wilson disease may also present with additional complications such as acidosis, aminoaciduria, and disturbances in electrolyte levels [7]. In severe cases of Wilson disease, indirect complications can arise, potentially leading to acute kidney injury. These complications may include bile cast nephropathy, rhabdomyolysis, and, in the most severe instances, massive acute hemolysis [8].

In a study by Shankar et al., a case involving a

21-year-old man with bipolar affective disorder was documented. The patient presented four years later with hypokalemic quadriparesis alongside both proximal and distal renal tubular acidosis. Upon ophthalmologic examination using a slit lamp, the presence of Kayser-Fleischer rings was confirmed. Subsequent diagnosis of Wilson disease was established through assessments of serum ceruloplasmin levels and 24-hour urinary copper levels. This case highlights the importance of considering Wilson disease in patients presenting with unexplained neurological and renal symptoms, even in the hepatic involvement absence [9].

In a study by Saiteja et al., an 11-year-old girl with vitamin-D-refractory rickets was described. Notably, this case presented without hepatic or neurological involvement upon admission. However, given the family history of an elder sister exhibiting rigidity with cognitive and speech impairment, an ophthalmic evaluation using a slit lamp examination was conducted. The examination revealed bilateral Kayser-Fleischer rings, prompting further investigation. Subsequent assessments indicated low serum ceruloplasmin levels and elevated 24-hour urinary copper levels in the index case. Additionally, the patient displayed normal anion gap metabolic acidosis, along with hypokalemia and hyperchloremia [3].

Palkar et al. documented the case of two sisters, aged 15 and 13, who exhibited bowed legs that progressed over time, leading to walking difficulties. The suspicion of Wilson disease arose due to the presence of splenomegaly, indicating portal hypertension, and the observation of Kayser-Fleischer rings during slit lamp examination [10]. The studied patient had a history of ataxia and dysarthria preceding loss of consciousness. Laboratory findings revealed tubulopathy characterized by glucosuria and hypercalciuria. Further evaluation revealed low serum ceruloplasmin levels and elevated 24-hour urinary copper levels that finally showed the neurological and renal manifestations of Wilson disease.

In Conclusion

In summary, Wilson disease should be considered as a multisystem disease with potential neurological and renal involvement from the outset. Comprehensive evaluation, including neurologic and renal assessment, should be integrated into the diagnostic workup of Wilson disease to facilitate timely diagnosis and management of neurologic and renal complications.

Acknowledgment

None.

Authors' Contribution

Toktam Moosavian was primarily responsible for the management of the patient. She also contributed to the elaboration, drafting, and final approval of the work alongside Shiva Fatollahierad. Zahra Pournasiri provided expertise in managing kidney complications, offered professional guidance, and participated in the drafting and final approval of the work.

Conflict of Interest

None.

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