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Case report

Partial status epilepticus induced by hypocupremia in a patient with Wilson's disease

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ABSTRACT

Although seizures are rarely encountered in Wilson's disease (WD), seizures related to hypocupremia have not been reported before. We report a patient presenting with partial status epilepticus who was on strict low-copper diet and chelating therapy for WD. Despite other rare causes of seizures in WD including penicillamine-induced pyridoxine deficiency, cerebral copper deposition and metabolic encephalopathy, the most probable cause of resistant status epilepticus in this patient was found as hypocupremia from overzealous treatment. This case examplifies that hypocupremic states should be kept in mind as a risk factor for resistant seizures.

1. Introduction

Epileptic seizures have been reported to occur in about 6% of patients with Wilson's disease (WD), starting shortly after the initiation of chelator therapy and responding well to antiepileptic treatment.[1,2] Status epilepticus in WD after starting the treatment with penicillamine is reported only in one patient in the literature, where hypocupremia was present though not blamed for seizures.[1] Seizures related to hypocupremia have not previously been reported in the literature. Here, we present a patient with Wilson's disease under strict low-copper diet and chelating treatment, who was admitted to our hospital due to partial status epilepticus.

2. Case report

A 21-year-old male patient was brought to our emergency unit because of recurrent convulsions. The patient was being followed-up with the diagnosis of Wilson's disease for five years in another center. He was under treatment with zinc (100 mg/day), D-penicillamine (1200 mg/day), and multivitamins ($B_1/B_6/B_{12}$ 250/250/1000 mg/day) in addition to a very strict low-copper diet. Seven months ago, the patient had experienced difficulties in speaking, swallowing and walking, upon which the dosage of D-penicillamine was increased and the patient was told to obey his diet strictly. Few weeks after these changes in his treatment, he started to have rapid, jerky contractions over his left arm and leg. At that time, copper level was measured as 17.5 μg/dl in serum, and 2485.6 μg/dl in 24-h urine. But nevertheless, the dosage of D-penicillamine and zinc was increased to treat these contractions and trihexyphenidyl (15 mg/day) was added to the therapy. After these arrangements, the contractions over his left arm and leg showed a prominent deterioration, and he had two consecutive secondarily generalized seizures, upon which he was admitted to our emergency department and hospitalized.

At his admission to our hospital, he was apathic with limited cooperation. His speech was dysarthric and hypophonic, he had drooling with a fixed open-mouth smile. He had bilateral hand tremor, truncal ataxia and unsteady gait. He also had generalized bradykinesia and dystonia being more prominent on his right side, getting worse with voluntary movements. Other than Wilson's disease, his past medical history was unremarkable. There was a first-degree consanguinity between his parents. He had two healthy brothers (25 and 28 years).

During his stay in hospital, he continuously had partial seizures as clonic contractions over his left arm and leg, some of which showed secondary generalization manageable with intravenous diazepame only. Multiple electroencephalograms (EEG) revealed diffuse slowing and multifocal left temporo-parieto-occipital and right centro-frontal epileptiform activity characterised by rhythmic, sharp-contoured theta waves intermixed with fast activity. Ictal EEG performed at the time of left-sided contractions also revealed bifrontal epileptiform activity being more prominent on the right side (Fig. 1). He was started on oral levetiracetam therapy, which was increased up to 1000 mg/day without any benefit. The therapy was then changed to diphenylhydantoin, which has also failed in seizure control in spite of high doses (500 mg/day). Although he was already on multiple vitamin B supplementation, high doses of intravenous multiple vitamin B replacement therapy

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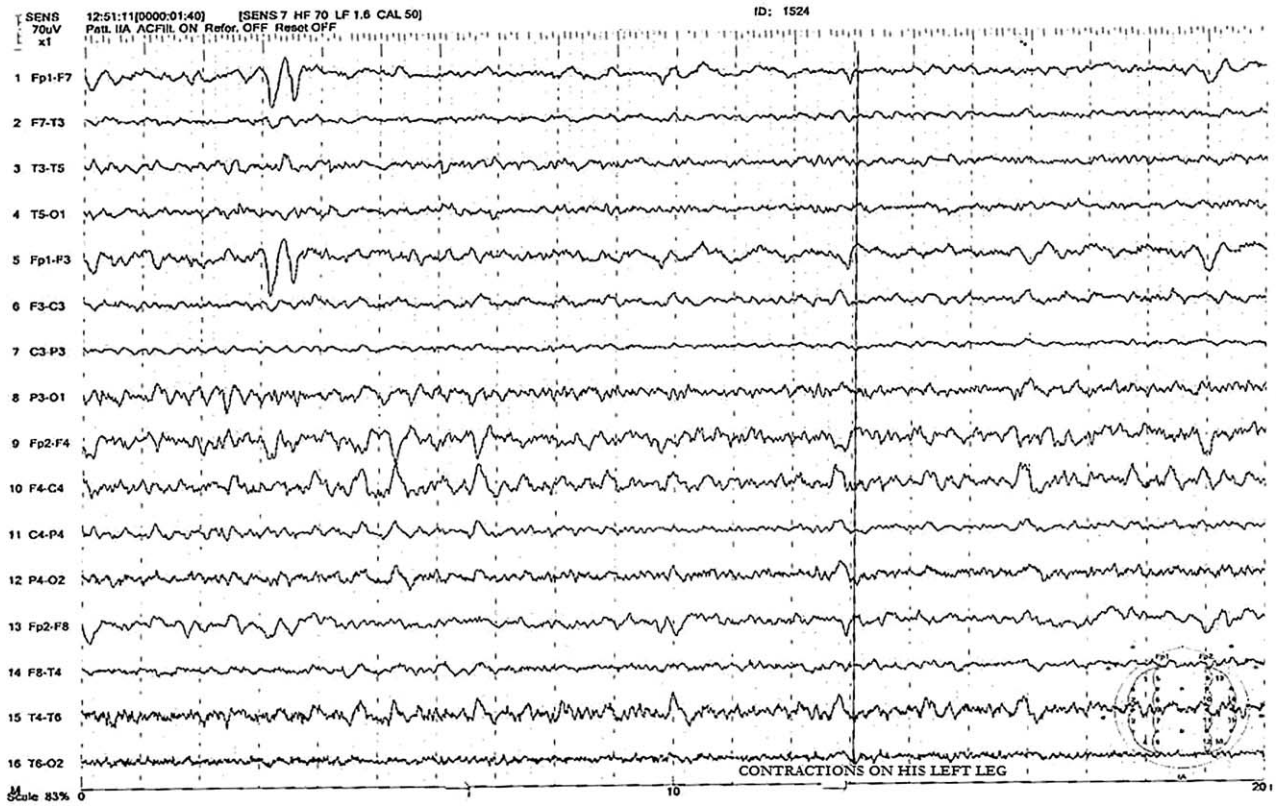

Fig. 1. Ictal EEG demonstrates bifrontal epileptiform activity being more prominent on the right side.

were given but failed to stop or even diminish the seizures. None of the antiepileptic drugs as levetiracetam and diphenylhydantoin nor palliative measures as vitamin B replacement therapy were effective on resistant seizures. Interestingly, the partial status epilepticus was aborted only on administration of intravenous diazepame.

The cranial magnetic resonance imaging (MRI) of the patient performed five years ago at the time of diagnosis of WD showed generalized subcortical demyelination as hyperintense signal changes over bilateral parietotemporal subcortical white matter, and prominent atrophy in supratentorial deep white matter with ventricular dilatation in T2 and Flair weighted images. The repeated cranial MRI during hospitalization revealed that bilateral putamen, mesencephalon, bilateral middle and superior cerebellar peduncles were also affected in addition to a more diffuse subcortical involvement (Fig. 2).

Laboratory investigations excluded any known metabolic or infectious causes of convulsions, including serum calcium, magnesium and pyridoxine levels. On the other hand, his serum copper level was measured as low as 2.2 μg/dl (normal value: 85–190 μg/dl) and copper level in 24-h urine was measured as 165.3 mg/day (normal value: 3–35 mg/day). Upon these findings, we stopped D-penicillamine and zinc therapy, and encouraged the patient to have a high-copper diet. The seizures diminished distinctly and ceased within few days, and diazepame therapy was gradually withdrawn in a week. His serum copper level was increased to 15 μg/dl. At this stage, his speech and swallowing also showed some improvement, he became able to walk without any assistance. Bradykinesia and right-sided action dystonia were still present. He was discharged with zinc therapy only (150 mg/day). A free diet and weekly measurements of serum copper level were recommended. After five months of his admission, serum copper level was 13.7 μg/dl, copper level in 24 h urine was 135 μg/dl, and he was still seizure-free.

3. Discussion

Epileptic seizures are reported to be rare in Wilson's disease occurring in about 6–7% of cases, and to respond well to antiepileptic treatment.[1,2] Status epilepticus in WD was reported only in one patient in the literature, which was reported to develop

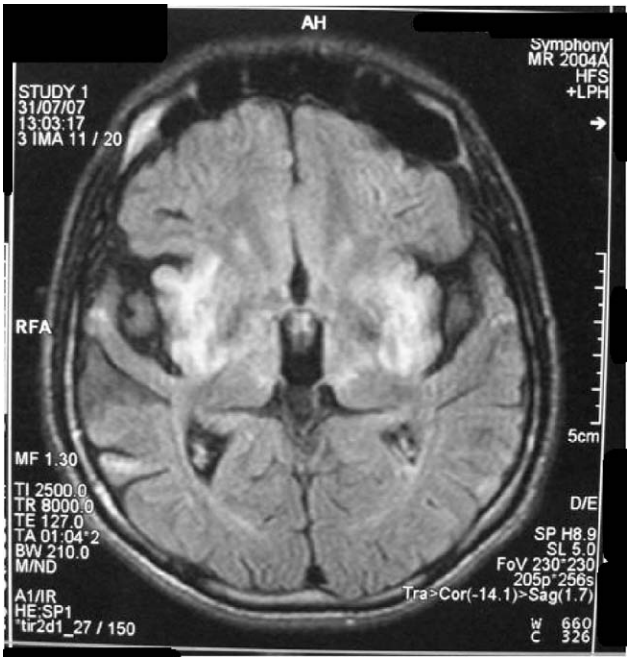

Fig. 2. The axial T1-weighted cranial MRI reveals the involvement of bilateral putaminal structures observed as hyperintense signal changes.

after the treatment with penicillamine.[1] In that case, hypocupremia was present though it was not accused of seizures. Mechanisms proposed to be responsible for increased seizure activity in WD include penicillamine causing pyridoxine deficiency,[3] direct effect of copper deposition,[4] or metabolic encephalopathy and pathological changes.[5] The possible effect of D-penicillamine on pyridoxine deficiency was not accepted as the cause of resistant seizures in this patient in the presence of a normal pyridoxine level, and also because seizures did not respond at all to multiple vitamin B replacement therapy or the cessation of D-penicillamine treatment.

Although copper deposition in various parts of cerebral cortex was proposed to play a role in epileptogenetic processes in some patients with WD, cerebral changes were not thought to be responsible from status epilepticus in our patient. Besides, the MRI findings of our patient were in consistent with hypocupremia, an important complication rarely encountered in Wilson's disease, resulting from overzealous treatment.[6] These central nervous system changes include bilateral symmetrical demyelinating lesions in caudate, putamen, substantia nigra, tegmentum, and thalamus. The authors defining these MRI features have linked them to hypocupremia and have suggested copper monitorization.[6]

Seizures related to hypocupremia have not been reported before in the literature. Copper is a component of key metalloenzymes that have a critical role in the structure and function of the nervous system. These include cytochrome-*c* oxidase for electron transport and oxidative phosphorylation in the mitochondrial respiratory chain, copper–zinc superoxide dismutase for antioxidant defense, tyrosinase for melanin synthesis, dopamine hydroxylase for catecholamine biosynthesis, and ceruloplasmin for brain iron homeostasis. Reduction in cytochrome oxidase activity may be the likely basis for neurological dysfunction associated with the copper deficient states.[7] In Menkes disease, which is an X-linked genetic disorder of intracellular copper transport, impaired activity of various copper-dependent enzymes causes the clinical table, and epileptic seizures are well-known features of the disease. In one case report, treatment with copper replacement therapy has been shown to be effective in seizure control in a patient with Menkes disease.[8] On this basis, we propose that impaired activity of copper-dependent enzymes might have led to the resistant status epilepticus in our patient during hypocupremic state.

In conclusion, we have a patient with a very low serum copper level due to overzealous treatment of Wilson's disease, who presented with resistant partial status epilepticus responsive to oral diazepame only. These resistant seizures ceased only after the serum copper level has reached to normal values. This novel case examplifies that hypocupremic states should be kept in mind as a risk factor for resistant seizures, especially in patients at risk such as Wilson's disease. In addition, serum copper levels should therefore be monitored to prevent further neurological complications secondary to copper deficient states.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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