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Sodium Valproate-induced Adult-onset Type 2 Citrullinemia

Sodyum Valproat Kullanımı ile Tetiklenen Erişkin Başlangıçlı Tip 2 Sitrüllinemi

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Anahtar Kelimeler: Erişkin başlangıç, ensefalopati, sodyum valproat, tip 2 sitrüllinemi, üre siklus defektleri

Dear Editor,

Urea cycle defects (UCDs) have been recognized increasingly in adults presenting with acute encephalopathy who have been healthy before. Hyperammonemic crises can be precipitated by many reasons such as trauma, surgery, acute protein deprivation and sodium valproate use.

Herein, we report a patient with type 2 citrullinemia (CTLN2) with hyperammonemic encephalopathy induced by sodium valproate.

A 30-year-old male patient admitted to the emergency department with fever and loss of consciousness. He was weaker than his peers. As the patient did not speak Turkish and had no relatives with him, information about his diet, past medical history, occupation and consanguinity of his parents could not be obtained. Babinski sign was positive bilaterally. Complete blood count, serum electrolyte and mineral levels, kidney function tests and urinalysis were normal. Liver function tests showed mild elevation of aspartate aminotransferase and alanine aminotransferase. Chest radiography and electrocardiogram were normal. Cranial computed tomography was normal. Cranial magnetic resonance imaging (MRI) showed bilateral patchy contrast enhancement involving the frontal, temporal, and parieto-occipital lobes and leptomeningeal contrast enhancement on T2, FLAIR and T1 sequences (Figure 1A, B, C, D, E). Biochemical analyses of the cerebrospinal fluid (CSF) yielded normal findings and the CSF culture and herpes polymerase chain reaction test were both negative. Electroencephalography (EEG) showed abnormal background activity. The preliminary diagnosis of the patient was acute encephalitis and he was treated with intravenous acyclovir (2250 mg/day) and oral oseltamivir (150 mg/day). He had a generalized tonic-clonic seizure on the 3rd day of admission. After the first seizure, he had two more seizures on the 4th and 6th days of admission. All of the seizures had the same clinical pattern.

In the neuro-intensive care unit (NICU), he exhibited agitated periods lasting for 1-2 hours, especially during the evenings. The anti-seizure treatment consisted of levetiracetam (1500 mg per day), sodium valproate (1500 mg per day), and carbamazepine (400 mg per day) which were started and increased gradually. He was alert and mobile without support at the end of the treatment for encephalitis and was discharged on the 29th day of his admission.

Five days later, he was readmitted to the emergency room with loss of consciousness. On neurological examination stupor and bilateral pyramidal signs were found and he was transferred to the NICU.

Cranial MRI showed hyperintensities and new contrast enhancement in bilateral parieto-temporal cortical areas and basal ganglia on T2, FLAIR and T1 sequences (Figure 2A, B, C, D). CSF analyses were normal. Abnormal background activity and epileptiform activity on the left anterior temporal lobe were found in EEG. His blood ammonia level was 339 µmol/l (n=9-97 µmol/l). Although sodium valproate treatment was discontinued, hyperamonemia persisted. Arterial blood gas analysis showed respiratory alkalosis. Hyperammonemia and encephalopathy were treated with hemodiafiltration. Since diagnostic metabolic blood and urine samples were not collected in the acute period, they were within normal limits after hemodiafiltration treatment. During

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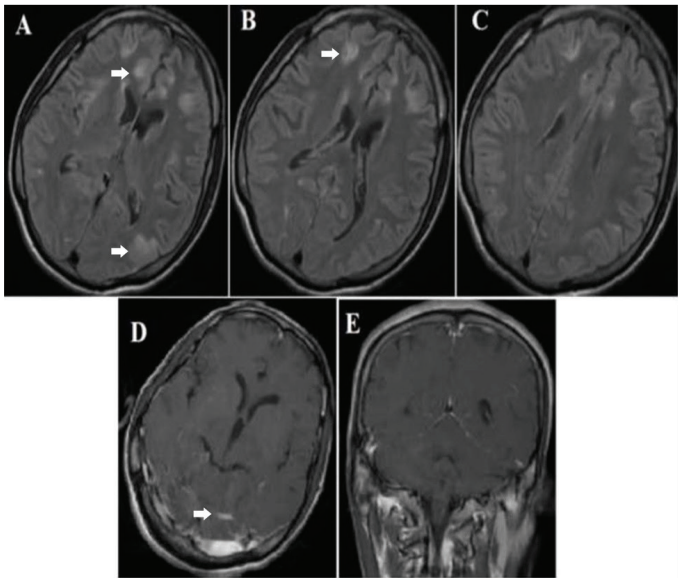

Figure 1. A, B, C) Bilateral hyperintense lesions involving the frontal, temporal and parietooccipital lobes on the axial T2 weighted and FLAIR images. D, E) Bilateral patchy contrast enhancement involving the frontal, temporal and parieto-occipital lobes and leptomeningeal contrast enhancement on axial and coronal T1 weighted images

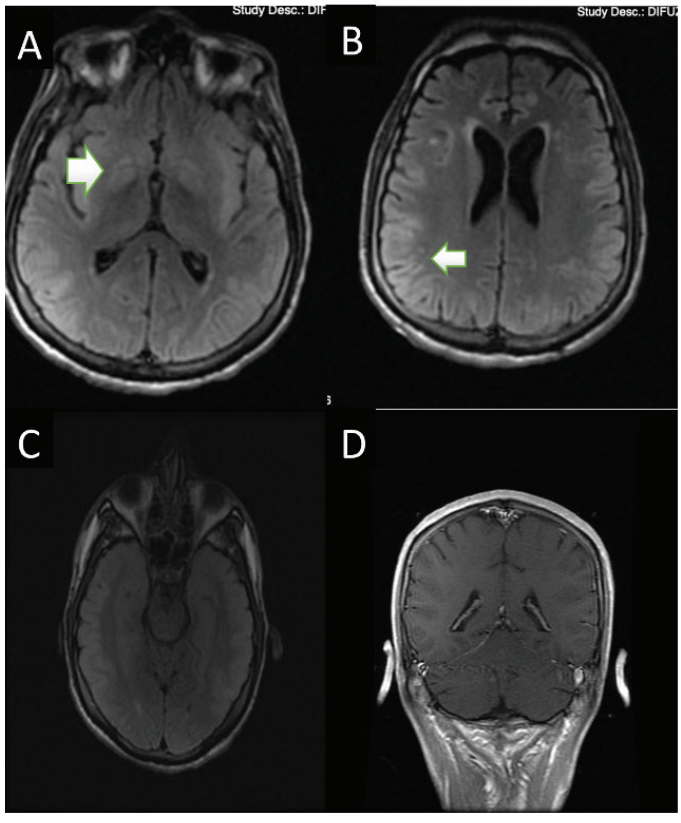

Figure 2. A, B, C, D) T2, T1 weighted and FLAIR images show hyperintensities and new contrast enhancement involving bilateral parieto-temporal cortical areas and basal ganglia

the 45 day period after onset encephalopathy had improved minimally and at the 46th day, he had another episode of loss of consciousness. Plasma amino acid analysis showed moderately elevated levels of plasma citrulline [142.2 mmol/l (range 17-46 µmol/l)] and threonine [312 mmol/l (range 60-200 µmol/l)] with increased threonine/serine ratio. Urinary orotic acid level was normal. Based on these metabolic abnormalities, CTLN2 was the strongly suspected diagnosis. Molecular analysis confirmed this diagnosis with a homozygous c.848 G> T (p. G283V) mutation on the *SLC25A13* gene. Sodium benzoate (250 mg/kg/day), L-arginine (5 g/day) and high-calorie diet with high protein and reduced carbohydrate consumption were started. However, the patient died due to nosocomial infection and subsequent septic shock.

CTLN2 is a rare inherited inborn error of urea cycle metabolism that affects men more than women (2.4:1). It is usually diagnosed between the ages of 20 and 70 years (1). *SLC25A13* gene mutations are responsible for the mitochondrial aspartate glutamate carrier defect causing the disease (2).

The CTLN2 is an autosomal recessive disorder characterized by hyperammonemia accompanied by recurrent episodes of neuropsychiatric manifestations, including nocturnal delirium, convulsive seizures and coma (3).

Our patient's ammonia level was normal at admission yet after dinner, when his ammonia levels increased, delirium and behavioral changes developed. Sodium valproate inhibits the activity of carbamoyl phosphate synthetase and causes hyperammonemia, therefore, it might have been the trigger in our patient.

Adults newly diagnosed with CTLN2 are recognized by elevated serum ammonia level, liver dysfunction, elevated serum citrulline and arginine levels and elevated threonine/serin ratio in serum. Detection of a mutation in the *SLC25A13* gene is the gold standard for diagnosis (4). Emergency management of hyperammonemic episodes in CTLN2 should include avoiding carbohydrates or glycerol infusions (5). A diet low in carbohydrates, rich in protein and lipids should be given, liver transplantation is also an option (6).

The MRI findings are hyperintense lesions on T2-weighted images in the cerebral white matter, cingulate gyri, temporal lobes and insular regions, pons, and cerebellar peduncles and also reversible areas of focal cerebral edema (7).

Sodium valproate for seizure treatment may be the trigger of hyperammonemia in our patient. There is not enough information in the literature about how sodium valproate might be a triggering factor for inital clinical presentation of CTLN2.

Clinicians should be aware of the fact that initial clinical presentation of UCDs can be observed in adulthood. Adult onset forms may present with neurobehavioral symptoms and seizures. In patients with unexplained encephalopathy, ammonia levels should be checked and drugs causing hyperammonemia should be discontinued.

Ethics

Informed Consent: Written consent was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.E.Ş., Ş.B., Concept: D.K., Ş.B., Design: B.E.A., R.E.Ş., Data Collection or Processing:

B.E.A., D.K., Analysis or Interpretation: T.D., Ş.B., Literature Search: B.E.A., Writing: B.E.A., T.D.

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