Citrullinemia type 1 (CTLN1) is a rare inherited urea cycle disorder, which resulted from the deficiency of argininosuccinate synthetase enzyme. We presented an infant who was hospitalized because of acute losses of tonus and cyanotic hypoventilation attacks lasting approximately 4–5 min. The physical and neurological examinations were normal. Ammonia level was in the normal range. Citrulline levels increased in both blood and urine. The blood sample was sent to mutation analysis, which showed one novel and one known mutation on ASS1 gene sequencing: a heterozygous novel mutation p.A94V (c.281C>T) and a heterozygous mutation p.W179R (c.535C>T). Urea cycle disorders should be considered in the differential diagnosis of unexplained brief apnea or hypoventilation attacks, even though those symptoms do not lead to hyperammonemia during infancy and childhood as seen in our patient. This is the first case in terms of atypical clinical presentation with a new mutation for CTLN1.

Keywords: Apnea, epilepsy, hyperammonemia, urea cycle disorders

Case Report

Citrullinemia with an Atypical Presentation: Paroxysmal Hypoventilation Attacks

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Citrullinemia type 1 (CTLN1) is a rare inherited urea cycle disorder, which resulted from the deficiency of argininosuccinate synthetase enzyme. We presented an infant who was hospitalized because of acute losses of tonus and cyanotic hypoventilation attacks lasting approximately 4–5 min. The physical and neurological examinations were normal. Ammonia level was in the normal range. Citrulline levels increased in both blood and urine. The blood sample was sent to mutation analysis, which showed one novel and one known mutation on ASS1 gene sequencing: a heterozygous novel mutation p.A94V (c.281C>T) and a heterozygous mutation p.W179R (c.535C>T). Urea cycle disorders should be considered in the differential diagnosis of unexplained brief apnea or hypoventilation attacks, even though those symptoms do not lead to hyperammonemia during infancy and childhood as seen in our patient. This is the first case in terms of atypical clinical presentation with a new mutation for CTLN1.

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Introduction

Citrullinemia type 1 (CTLN1 or citrullinemia classic, MIM215700) is a rare autosomal-recessive inborn error of urea metabolism, which resulted from the deficiency of argininosuccinate synthetase enzyme. The incidence is estimated to be 1 per 57,000 of live births. Infants are usually presented with severe attacks of hyperammonemia characterized by gastrointestinal and neurologic manifestations. However, considerable clinical variability was reported in different settings of the patients. Thus, mild or asymptomatic individuals have been detected in family studies and newborn screening programs. The diagnosis can be confirmed by plasma quantitative amino acid analysis with the absence of argininosuccinic acid, low arginine, and elevated citrulline and glutamine levels. We report an infant who has atypical presentation as paroxysmal brief–recurrent hypoventilation attacks with a new mutation for CTLN1.

Case Report

A 3-month-old baby, who experienced brief and several suspicious epileptic events, was presented by his family to outpatient clinic. When the history was evaluated in detail, it was found that he had been hospitalized because of three acute losses of tonus and cyanotic hypoventilation attacks lasting 4–5 min at 3 weeks of age. These attacks had been prediagnosed as epileptic spells with unremarkable electroencephalography (EEG) findings. He was then started on phenobarbital, and discharged with a stable condition. As to his remaining history, he was the second child born of a consanguineous marriage after an unremarkable antenatal period and delivery. Family history revealed that his brother had autism-spectrum disorder. At 3 months of age, he was admitted...
Öztürk, et al.: Citrullinemia with an atypical presentation

Citrullinemia is a rare urea cycle defect, which resulted from the deficiency of argininosuccinate synthetase, which is defined as a rate-limiting enzyme that catalyzes the third step in the cycle. Therefore, the function of argininosuccinate synthetase is catabolism and conversion of citrulline and aspartate to argininosuccinate. The late-onset form shows some episodes of altered consciousness, restlessness, and abnormal behavior during adulthood. The duration of hyperammonemic attacks of encephalopathy is generally expected to be days or weeks. Different from earlier reports, our patient presented with brief apnea–hyperventilation attacks with duration of minutes without hyperammonemia. Because of this unique presentation, the patient underwent some additional testing in differential diagnosis for epileptic or non-epileptic paroxysmal attacks. However, EEG was found to be normal, contrary to the expected EEG findings consisting of burst suppression, multifocal spikes, or repetitive paroxysmal activity at times of classical crisis of citrullinemia. Thanks to the analysis of plasma and urine amino acids, elevated levels of citrulline were detected, which proved useful in the diagnosis of citrullinemia. To confirm the disease, we studied and identified two mutations of ASS1. First, a heterozygous novel mutation was found in p.A94V (c.281C>T), which was not previously detected in any of the patients. Second, the gene showed a heterozygous mutation in p.W179R (c.535C>T), which was mostly detected in mild or asymptomatic patients from the Mediterranean countries including Turkey. It is quite unusual that the patient, who is an offspring born of a consanguineous marriage, carried two different mutations. So the parents were investigated, and the mother was found to be homozygous for p.W179R (c.535C>T) mutation and the father was heterozygous for p.A94V (c.281C>T) mutation. Protein-restricted diet and supplementation of arginine were started. The patient was back to outpatient visit at 4, 5, 6, 9, and 12 months of age without any further attacks or neurological deterioration. As the attacks stopped after the treatment of CTLN1, phenobarbital was tapered and discontinued at follow-up. Family was counseled to seek the mutation analysis of the other child, who was already diagnosed with autism. Blood for DNA extraction was analyzed and found to be normal for this sibling.

**Discussion**

Citrullinemia is a rare urea cycle defect, which resulted from the deficiency of argininosuccinate synthetase, which is defined as a rate-limiting enzyme that catalyzes the third step in the cycle. Therefore, the function of argininosuccinate synthetase is catabolism and conversion of citrulline and aspartate to argininosuccinate. Classical CTLN1 has high mortality rate and poor neurological outcome because of hyperammonemic metabolic attacks. Although the clinical presentation can present with severe encephalopathy within days after birth in neonatal period, the infantile form usually manifests moderate-to-mild clinical course confining to recurrent episodes of lethargy, acute ataxia, hyperactivity, vomiting, and dehydration, which potentially can lead to coma. The late-onset form shows some episodes of altered consciousness, restlessness, and abnormal behavior during adulthood. The duration of hyperammonemic attacks of encephalopathy is generally expected to be days or weeks. Different from earlier reports, our patient presented with brief apnea–hyperventilation attacks with duration of minutes without hyperammonemia. Because of this unique presentation, the patient underwent some additional testing in differential diagnosis for epileptic or non-epileptic paroxysmal attacks. However, EEG was found to be normal, contrary to the expected EEG findings consisting of burst suppression, multifocal spikes, or repetitive paroxysmal activity at times of classical crisis of citrullinemia. Thanks to the analysis of plasma and urine amino acids, elevated levels of citrulline were detected, which proved useful in the diagnosis of citrullinemia. To confirm the disease, we studied and identified two mutations of ASS1. First, a heterozygous novel mutation was found in p.A94V (c.281C>T), which was not previously detected in any of the patients. Second, the gene showed a heterozygous mutation in p.W179R (c.535C>T), which was mostly detected in mild or asymptomatic patients from the Mediterranean countries including Turkey. It is quite unusual that the patient, who is an offspring born of a consanguineous marriage, carried two different mutations. So the parents were investigated, and the mother was found to be homozygous for p.W179R (c.535C>T) mutation and the father was heterozygous for p.A94V (c.281C>T) mutation.

The presence of a high level of ammonia can result in cerebral edema and lead to neurological deteriorations. MRI findings in the neonatal period comprise cortical involvement accompanied by signal intensity changes in the basal ganglia and diffusion restriction in extensive brain areas involving the basal ganglia, midbrain, dorsal portions of the pons, and middle cerebellar peduncle. However, in our patient, MRI was performed in the neonatal period, and it revealed normal results. These findings were consistent with no brain damage during these episodes. Furthermore, no detectable hyperammonemic crises were developed in our patient. Mild clinical outcome of compound heterozygous mutations found in different ethnic backgrounds is characterized by the residual activity of argininosuccinate synthetase. However, in patients with compound heterozygous variants, genotype–phenotype correlation is not very strong in case serials. The management of hyperammonemic encephalopathy includes emergent therapies such as sodium benzoate and sodium phenylbutyrate, which divert ammonia.

Plasma amino acids revealed elevated citrulline levels, 551 (16–32) Umol/L. Excretion of citrulline levels markedly increased in urinary amino acid analysis (752 Umol/L [0–10]). Mutation analysis for the argininosuccinate synthetase 1 (ASS1) gene was performed by whole-genome sequencing. One novel and one known mutation were identified on ASS1 gene sequencing: a heterozygous mutation p.A94V (c.281C>T) and a heterozygous mutation p.W179R (c.535C>T), which led to the diagnosis of CTLN1. The parents were investigated for heterozygosity. Mother was homozygous for p.W179R (c.535C>T) mutation and father was heterozygous for p.A94V (c.281C>T) mutation. Protein-restricted diet and supplementation of arginine were started. The patient was back to outpatient visit at 4, 5, 6, 9, and 12 months of age without any further attacks or neurological deterioration. As the attacks stopped after the treatment of CTLN1, phenobarbital was tapered and discontinued at follow-up. Family was counseled to seek the mutation analysis of the other child, who was already diagnosed with autism. Blood for DNA extraction was analyzed and found to be normal for this sibling.

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into alternative pathways, hemodialysis, and peritoneal dialysis. Furthermore, protein-restricted diet is also suggested to prevent attacks and neurological deterioration; and consistent with this argument, our patient was started on this treatment and no further attacks of apnea along with normal neurological development were observed at follow-up. We suggested that early diagnosis and treatment may protect the patient from apnea attacks and provide normal neurological development.

**Conclusion**

Urea cycle disorders should be considered in the differential diagnosis of unexplained brief apnea or hypoventilation attacks, despite no long duration of episodes and hyperammonemia during infancy and childhood as seen in our patient. We reported a case with a novel CTLN1 mutation in p.A94V (c.281C>T), which is a rare presentation of brief hypoventilation episodes. To the best of our knowledge, this is the first case according to the clinical findings with a novel mutation for CTLN1.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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