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Arginase deficiency with parotid gland swelling and hyperamylasemia: A case report

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Abstract

Arginase deficiency is a progressive neurological disorder characterized by episodic hyperammonemia crises. Our patient had been diagnosed with cerebral palsy (spastic paraplegia) in childhood and received rehabilitation. She had suffered parotid swelling since the age of 5 years, prior to liver dysfunction becoming apparent, and then developed hyperamylasemia at 8 years of age. At age 25 years, she presented with hyperammonemia and elevations of aspartate aminotransferase and alanine aminotransferase. At age 27 years, she was diagnosed with arginase deficiency due to hyperargininemia and absent arginase activity in erythrocytes. Liver cirrhosis was also present. She was hospitalized several times for management of episodic hyperammonemia due to recurrent viral infections, an unbalanced diet, and poor compliance with medications.

Keywords

Arginase deficiency, parotid gland swelling, hyperamylasemia, hyperammonemia, liver cirrhosis

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Introduction

Arginase deficiency is a rare autosomal recessive urea cycle disorder characterized by hyperargininemia, episodic hyperammonemia, spastic paraplegia, progressive neurological impairment, and developmental delay.[1,2] Most patients with arginase deficiency begin to show symptoms between the ages of 1 and 5 years. These most common clinical presentations include spasticity, feeding problems, poor growth, seizures, developmental delay, and intellectual disability.[1,2] Herein, we describe a patient with arginase deficiency associated with parotid swelling and hyperamylasemia. To date, one case of arginase deficiency with parotid enlargement has been reported.[3] Chronic swelling of the parotid gland occurs mainly in patients with alcoholic liver cirrhosis, malnutrition, inflammation, neoplasms, and allergies.[4,5] In animal experiments, argininemia reportedly stimulated the release of amylase from rat parotid cells.[6]

Case report

The patient was a 32-year-old woman with severe intellectual disability, spastic paraplegia, and liver cirrhosis. Her maternal grandmother and paternal great-grandfather were siblings. Development had been normal during the neonatal period, but developmental delay was later recognized (sitting: 8–9 months; walking: 2 years, 1 month). Spastic paraplegia was diagnosed, and she underwent rehabilitation. At the time of her first visit to our department, she was 8 years and 9 months of age. Her chief complaints were nausea and vomiting. At that time, bilateral parotid swelling (size 4 cm × 6 cm, elastic, hard, but without tenderness) had been observed since age 5 years, and blood amylase was elevated (200 U/L; reference range: 44–132 U/L). Subsequently, blood amylase rose to an approximate range of 400–2000 U/L (pancreatic [P]-type: salivary [S]-type = 20%–30%: 70%–80%; reference range: P: S = 45%–50%: 50%–60%). Amylase levels tended to increase in conjunction with bilateral parotid swelling. At the age of 10 years, contrast sialography showed only mild dilation of the end of the glandular parenchyma with neither calculus nor abnormalities of the

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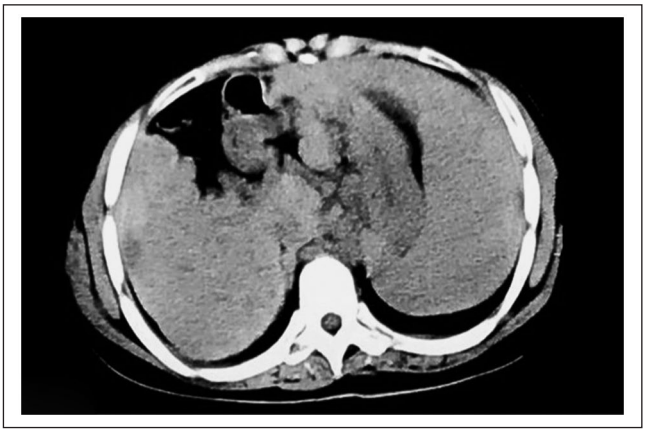

Figure 1. CT scan of the abdomen with contrast enhancement at age 30 years. CT scan shows the marked splenomegaly.

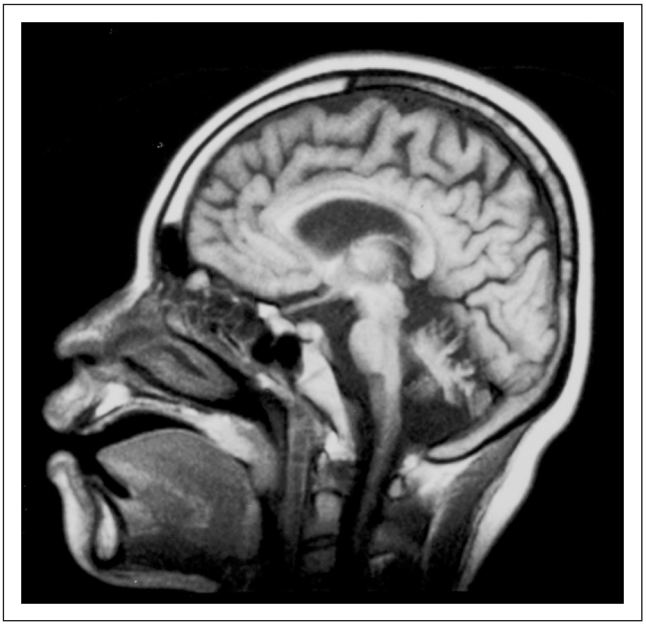

Figure 2. Brain MRI (sagittal T1-weighted) at age 27 years. MRI shows the atrophy of the cerebellum and cerebrum.

stellate duct, and biopsy of the parotid gland showed normal histology. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in serum were 37 U/L (reference range: 13–30 U/L) and 16 U/L (reference range: 7–23 U/L), respectively. All other laboratory findings, with the exception of amylase, were within normal ranges. The Tanaka-Binet Intelligence Scale[7] was 24 (intellectual disability: severe) at the age of 10 years. Neurological abnormalities progressively worsened, and she was wheelchair-bound by age 20 years. At age 25 years, her laboratory data were as follows: AST 61 U/L, ALT 67 U/L, ammonia 125 μg/dL (reference range: 12–66 μg/dL), amylase 1610 U/L (P: S 21%:79%). At age 27 years, she was hospitalized for vomiting and consciousness disturbance, caused by hyperammonemia (306 μg/dL) accompanied by convulsions. At that time, other laboratory data were as follows: white blood cell count 2.0 $\times$ 10^3/μL (reference range: 3.3–8.6 $\times$ 10^3/μL), red blood cell count 381 $\times$ 10^4/μL (reference range: 3.9–4.9 $\times$ 10^6/μL), hemoglobin 9.4 g/dL(reference range: 11.6–14.8 g/dL), platelets 49 $\times$ 10^3/μL (reference range: 158–348 $\times$ 10^3/μL), total protein 5.7 g/dL (reference range: 6.6–8.1 g/dL), albumin 2.4 g/dL(reference range: 4.1–5.1 g/dL), total bilirubin 2.1 mg/dL(reference range: 0.1–1.0 mg/dL), amylase 675 U/L, AST 177 U/L, ALT 166 U/L, prothrombin time 20.8 s (reference range: 10.5–13.5 s), and activated partial thromboplastin time 44.2 s (reference range: 24.5–36 s), while all markers for hepatitis were within normal ranges. Hyperargininemia (501.8 nmol/mL; reference range: 70–160 nmol/mL) was confirmed. The patient's erythrocyte arginase activity was 0%, whereas her parents had values of approximately 50%. Based on these findings, we diagnosed arginase deficiency. A low-protein diet (0.7–0.8 g/kg/day), arginine-free essential amino acid formula (7.5 g/day), and sodium benzoate (250 mg/kg/day) were started. Her consciousness improved, but the hyperargininemia (353–573 nmol/mL) persisted. Abdominal echography and computed tomography (CT) showed liver cirrhosis and splenomegaly (Figure 1). Brain magnetic resonance imaging (MRI) showed atrophy of the cerebellum and the cerebrum (Figure 2). Despite various treatments, including protein restriction, she had recurrent episodes of consciousness disturbance with hyperammonemia due to recurrent viral infections, an unbalanced diet (mayonnaise was her preferred food and she avoided carbohydrates), and poor compliance with medications.

Discussion

Hyperammonemia can be demonstrated in the blood of patients with urea cycle disorders. Blood ammonia levels above 360 μmol/L are associated with brain damage and severe developmental consequences.[8] The main strategies for managing urea cycle disorders are a protein-restricted diet, administration of oral nitrogen scavenging drugs, dietary supplementation with an arginine-free essential amino acid formula, hemodialysis, and liver transplantation.[1,2,8] Our patient had developed spastic paraplegia during childhood, which was followed up under a diagnosis of cerebral palsy. Similar to our case, other reports have described patients with arginase deficiency who were followed up for cerebral palsy and thus not diagnosed and treated appropriately at an early stage.[2,3] Parotid swelling had been observed since our patient was 5 years old, and hyperamylasemia with an increased S-type ratio was confirmed at the time of her first visit to our department. Hyperammonemia and subsequent hyperargininemia and the absent arginase activity were confirmed at age 27 years, leading to a diagnosis of arginase deficiency. In addition, she had liver cirrhosis. There are previous reports of cirrhosis in patients with arginase deficiency.[9,10]

Chronic parotid swelling is observed mainly in patients with alcoholic liver cirrhosis, malnutrition, inflammation, neoplasm, and allergies.[4,5] In our case, liver cirrhosis developing at around

age 27 years may have been the cause of parotid swelling, but there had been no evidence of cirrhosis at 8 years of age. In addition, the parotid swelling in our case clearly paralleled the severities of hyperargininemia and hyperammonemia. According to our literature search, there is only one similar report.[3] The cause of parotid swelling in our patient thus remains unknown.

Hyperamylasemia is mainly seen in patients with pancreatitis and parotitis. Hyperamylasemia of S-type isoamylase occurs with parotitis, obstruction of the parotid gland, and liver failure.[11] Our patient had chronic parotid swelling, but there were no apparent abnormalities in the parotid gland. In an animal study, Blachier et al.[6] showed L-arginine and L-ornithine to stimulate amylase release from rat parotid cells. L-Arginine is catabolized via two pathways in the rat parotid gland. In the major pathway, L-arginine is converted into urea and L-ornithine. In the minor pathway, L-arginine is converted directly into L-citrulline though to a limited extent. Arginine accumulates in arginase deficiency. However, the mechanism underlying the stimulation of amylase release has yet to be clarified.[6] In our case, high concentrations of L-arginine presumably stimulated the parotid gland for a prolonged period and increased amylase secretion from the parotid gland, which may have been responsible for the observed swelling of the parotid gland. Cornelius et al.[3] speculated that patients with arginase deficiency have elevated arginine in the salivary glands, augmenting nitric oxide synthesis, thereby leading to increased susceptibility of the salivary glands to oxidative damage, and ultimately causing enlargement.

In the acute stage of hyperammonemia, patients with arginase deficiency are treated with a carbohydrate rich diet, sodium benzoate, with or without sodium phenyl acetate, restricted protein intake, an arginine-free essential amino acid formula, and hemodialysis.[1,2,8] For maintenance, patients are managed with oral nitrogen scavenging drugs, restricted protein intake, and liver transplantation to reduce recurrent hyperammonemia.[1,2,8] Despite ongoing treatment with sodium benzoate, restricted protein intake, and an arginine-free essential amino acid formula, our patient had recurrent episodes of consciousness disturbance with hyperammonemia. This may have been due to recurrent viral infection, an unbalanced diet, and poor compliance with medications. Prior reports have suggested that early diagnosis and treatment of this disease may improve outocomes.[2,12]

In general, arginase-deficiency symptoms, such as sever spasticity, seizures, failure to thrive and intellectual disability, worsen later in life.[13] These neurological symptoms cannot be explained solely by hyperammonemia in cases with arginase deficiency. Arginine is a precursor for the synthesis of nitric oxide and guanidine compounds. Arginine and its metabolites, the guanidine compounds, are speculated to play roles in neurological impairment.[13,14] In addition, brain MRI of patients with arginase deficiency demonstrates atrophy of both the cerebellum and the cerebrum.[3,15] The MRI findings in our present patient were consistent with these prior observations.

Conclusion

Our patient had been diagnosed with spastic paraplegia in childhood, and subsequently presented with chronic bilateral parotid gland swelling and hyperamylasemia. In adulthood, she had been diagnosed with arginase deficiency and liver cirrhosis. The intellectual and motor disabilities in our case were likely exacerbated by the lack of an accurate diagnosis and appropriate treatment in early childhood.

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Author contributions

N.K., S.N., A.M., K.E. and H.M. evaluated the patient clinically. N.K. and S.N. wrote the manuscript. M.O. provided conceptual advice. All authors read and approved the final manuscript.

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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