DOI: 10.4274/tpa.46.15

Argininosuccinic aciduria in a neonate presented with inspiratory stridor

Emrah Can, Ali Bülbül, Sinan Uslu, Asiye Nuhoğlu*

Şişli Etfal Education and Research Hospital, Neonatal Clinic, İstanbul, Turkey

Şişli Etfal Education and Research Hospital, Neonatal Clinic, İstanbul, Turkey

Summary

A newborn who was brought with a clinical finding of severe inspiratory stridor was diagnosed with argininosuccinic aciduria after laboratory tests. This case is presented because it is the first case in whom inspiratory stridor was found as a clinical finding in argininosuccinic aciduria. The study was aimed to emphasise metabolic disease screening in newborns with inspiratory stridor without anatomic pathology. *(Turk Arch Ped 2011; 46: 81-3)*

Key words: Argininosuccinic aciduria, inspiratory stridor, newborn

Introduction

Argininosuccinic aciduria (OMIM-207900) is an autosomal recessive disease characterized with argininosuccinate lyase enzyme deficiency which is classified as an urea cycle disorder. Due to enzyme deficiency argininosuccinic acid (ASA) and ammonia accumulate in body fluids (1). The deficiency was firstly defined in 1958 by Allan et al. (2). Its incidence has been reported to be 1/70 000-91 000 (3). Urea cycle disorders are usually characterized with hyperammonemia, encephalopathy and clinical findings of respiratory alkalosis and have three forms defined according to different genetic mutations (4). In newborns, signs develop in the first week of life and usually in the first 24-72 hours in a healthy newborn baby with normal birth weight. Frequently, first signs include feeding intolerance, vomiting, lethargy, irritability, hypothermia and hyperventilation. Clinical deterioration proceeds rapidly and leads to damage to central nervous system and autonomic nervous system. In the neonatal period, patients are frequently lost in two weeks (5). The second form starts in the early infancy and proceeds slowly. Clinical characteristics of this form include mental and motor retardation, repeated convulsions, change of consciousness, hepatomegaly, skin lesions and "trichorrhexis nodosa" (6). The third form is the subacute or late-onset type and signs occur in infancy, childhood or puberte. The most prominent characteristics of the late-onset type include mental retardation, intermittent ataxia and intermittent hyperammonemia (2). This article presents a case diagnosed with argininosuccinic aciduria in the neonatal period with a clinical sign of severe stridor.

Case report

Baby A. was born by cesarian section because of cephalopelvic disproportion at the 39th gestational week as the first baby of an eighteen year old mother. Apgar scores were 8 and 10 at the 1st and 5th minutes. The baby was brought to the emergency department on the third day of life because of restlessness and rejection of feeding. On the first evaluation, severe stridor and tachypnea were found and the baby was hospitalized in the neonatal intensive care unit. The mother and father were first degree cousins. Prenatal follow-up was done regularly and no problem was found. On physical examination, weight was found to be 3450 g, height was found to be 49 cm and head circumference was measured as 33 cm. Respiratory examination revealed tachypnea, nasal flaring, stridor and intercostal retractions. Heart

Address for Correspondence: Emrah Can MD, Şişli Etfal Education and Research Hospital, Neonatal Clinic, Şişli, İstanbul, Turkey
E-mail: canemrahcan@yahoo.com **Received:** 15.09.2009 **Accepted:** 22.03.2010

beat rate was 154/min/rythmic, respiratory rate was 80/min. Muscle tonus was increased and newborn reflexes were decreased. Complete blood count and biochemical tests were normal. Examination of blood gases revealed compensated respiratory alkalosis (pH:7.39 PCO_2:20 mmHg, HCO_3:11.9 mEq/L, BE:-10.7 mEq/L). When repeated blood gases were found to be pH: 7.21 PCO_2: 63.8 mmHg, HCO_3: 25.2 mEq/L, BE: -4.1 mEq/L, CPAP (continuous positive airway pressure) was started and then mechanical ventilatory support was applied. Chest graphy was normal. Nasogastric tube was found to proceed easyly through both nostrils. Endoscopic examination of the larynx performed considering vocal cord paralysis in the differential diagnosis was found to be normal. Tests performed for differential diagnosis of metabolic diseases were as follows: blood ammonia level: 244 µmol/L (normal <50 µmol/L), citrulline level: 184 µmol/L (normal 19-51 µmol/L) and urine argininosuccinic acid level: 337 mmol/mol creatinine (normal <4 mmol/mol creatinine). The patient was diagnosed as argininosuccinic aciduria.

Protein intake was limited starting sodium benzoate for hyperammonemia together with supportive treatment. On the following days, acute renal failure and then ventilator-associated pneumonia developed and MRCNS (meticillin resistant coagulase- negative Staphylococcus Aureus) grew in the blood culture. Patient died on the 11th day of life because of multi-organ failure.

Discussion

Clinical and biochemical differences in argininosuccinic aciduria vary depending on the amount of enzyme deficiency, level of neonatal hyperammonemia and degree of brain damage developed (7). In the subacute or late form in which enzyme level is not very low, intellectual disability, episodic vomiting, growth/developmental retardation and hepatomegaly are prominent (8). In cases occuring during the neonatal period, the first sign is usually feeding intolerance. Because of nonspecific findings, mostly sepsis is considered and treatment is planned accordingly. However, transient moderate respiratory alkalosis attacks are important in terms of diagnosis in cases occuring during the neonatal period (9). Clinical deterioration usually proceeds rapidly and autonomic dysfunction or dysfunction of the neuromotor system including vasomotor imbalance, hypothermia, apnea, loss of tonus and reflexes develop (6). The first clinical findings in our case were also feeding intolerance and restlessness. On physical examination, severe inspiratory stridor was prominent. Although respiratory alkalosis has been reported in cases with a diagnosis of argininosuccinic aciduria in the literature, inspiratory stridor has not been defined until now. Our case is the first case diagnosed with argininosuccinic aciduria with a clinical finding of inspiratory stridor in the neonatal period.

Prenatal diagnosis of argininosuccinic aciduria is made by chorionic villus biopsy and postnatal diagnosis is made by clinical and biochemical examination. The value of ammonia is frequently above 200 µmol/L. Glutamine, alanine and citrulline levels are increased in serum. The presence of argininosuccinic acid in urine is considered to be diagnostic (6). In our case, argininosuccinic acid level was high in urine together with increased ammonia and citrulline levels in the blood. The definite diagnosis of the disease is made by showing argininosuccinate lyase enzyme deficiency in erythrocytes or fibroblasts (1). Genetically, mutation can be determined on argininosuccinic acid lyase (ASL) enzyme code on the short arm of the 7th chromosome (7cen-q11.2) (9). Although genetic examination was planned in our case for definite diagnosis, genetic examination could not be performed because the family did not give consent.

Clinical improvement and development is usually not seen in patients with argininosuccinic aciduria in the neonatal period. Generally, intervening infections, metabolic imbalance, failure of the immune system and intensive invasive interventions lead to death (10). Newborns treated efficiently in the early period show a poor response to treatment and babies who are not treated early are lost because of brain and lung hemorrhage before the diagnosis of metabolic disease is made. Argininosuccinic aciduria has a good prognosis only in a small proportion of cases treated dynamically. In cases treated efficiently, blood ammonia level returns to normal limits, hepatomegaly regresses and growth and development can be fulfilled. However, neuromotor development is affected in these cases despite treatment and intellectual levels are found to be low in the long term (11).

Currently accepted treatment for patients with a diagnosis of argininosuccinic aciduria includes low-protein diet to decrease loading in the urea cycle and providing necessary essential amino acids and appropriate calorie intake (12). Supportive therapies with substances which will provide nitrogen to be used in other pathways including sodium benzoate and sodium phenylbutyrate should be added. Arginine is the most important essential amino acid affecting production negatively in argininosuccinic aciduria and therefore its deficiency should absolutely be compensated (10). For this objective, 1.2-2 g/kg/day protein diet containing 0.4-0.7 g/kg/day L-arginine should be given to the patients (2,6). While the initial dose of sodium benzoate is 250 mg/kg/day, in severe cases the dose can be increased up to 500 mg/kg/day. However, the most frequently seen side effects of this treatment include nausea, vomiting and irritability (6). Since infections can proceed rapidly in cases with a diagnosis of argininosuccinic aciduria, early hospitalization and use of IV antibiotics will significantly prevent deaths due to infections in these infants (2). Treatment of our case was adjusted as 1.5 g/kg/day protein and 0.5 g/kg/day L-arginine. Sodium benzoate was started with a dose of 250

mg/kg/day, but the dose could not be increased because of continued vomiting. Although the diagnosis was made early and treatment was initiated in our case, the patient was lost on the 11th day after birth because of ventilator-associated pneumonia and multi-organ failure (acute renal failure, hepatic failure and cardiac failure).

Inspiratory stridor in the neonatal period is frequently a finding of obstructive pathology of upper airways or larynx pathology. Although respiratory alkalosis has been found in cases with argininosuccinic aciduria in the neonatal period, a finding of inspiratory stridor has not been reported until now. Our case was reported because of its characteristic of being the first case of argininosuccinic aciduria diagnosed with a finding of inspiratory stridor. Consequently, presence of metabolic diseases should be considered in the differential diagnosis in newborns with inspiratory stridor without an anatomic cause.

Conflict of interest: None declared

References

1. Al-Sayed M, Alahmed S, Alsmadi O, et al. Identification of a common novel mutation in Saudi patients with argininosuccinic aciduria. J Inherit Metab Dis 2005; 28: 877-83. (Abstract) / (PDF)
2. Matsuda I, Nagata N, Matsuura T, et al. Retrospective survey of urea cycle disorders: Part 1. Clinical and laboratory observations of thirty-two Japanese male patients with ornithine transcarbamylase deficiency. Am J Med Genet 1991; 38: 85-9. (Abstract)
3. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr 1996;43:127-70. (Abstract)
4. Walker DC, McCloskey DA, Simard LR, McInnes RR. Molecular analysis of human argininosuccinate lyase: mutant characterization and alternative splicing of the coding region. Proc Natl Acad Sci U S A 1990; 87: 9625-9. (Abstract) / (PDF)
5. Brusilow SW, Horwich AL. Urea cycle enzymes. In: Scriver CR, Beaudet AL, Sly WS, Valle D, (eds); Childs B, Kinzler KW, Vogelstein B, (assoc. eds). The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill, 2001: 1909-64.
6. Fernandes J, Saudubray J M, Van Den Berghe G, Walter J H. Disorders of the urea cycle and related enzymes. Inborn metabolic diseases: Diagnosis and treatment. 4th ed. Berlin: Springer, 2006: 265-72.
7. Gropman AL, Batshaw ML. Cognitive outcome in urea cycle disorders. Mol Genet Metab 2004; 81: 58-62. (Abstract) / (PDF)
8. Newnham T, Hardikar W, Allen K, et al. Liver transplantation for argininosuccinic aciduria: clinical, biochemical, and metabolic outcome. Liver Transpl 2008; 14: 41-5. (Abstract) / (PDF)
9. Trevisson E, Salviati L, Baldoin MC, et al. Argininosuccinate lyase deficiency: mutational spectrum in Italian patients and identification of a novel ASL pseudogene. Hum Mutat 2007;28: 694-702. (Abstract) / (PDF)
10. Urea Cycle Disorders Conference group. Consensus statement from a conference for the management of patients with urea cycle disorders. J Pediatr 2001; 138: 1-5. (PDF)
11. Batshaw ML, MacArthur RB, Tuchman M. Alternative pathway therapy for urea cycle disorders:twenty years later. J Pediatr 2001; 138: 46-54. (PDF)
12. Leonard JV. The nutritional management of urea cycle disorders. J Pediatr 2001;138:40-4. (Abstract)