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A Case of Biotinidase Deficiency in an Adult with Respiratory Failure in the Intensive Care Unit

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Background: Biotinidase deficiency (BD) is a rare, inherited autosomal recessive disorder that is treatable within childhood. We present a patient with pneumonia and respiratory acidosis who was not diagnosed with any systemic disorders; the patient was finally diagnosed as BD.

Case Report: A thirty-year-old woman was admitted to the emergency department with respiratory failure that had persisted for a few days and progressively weakening over the previous six months. Then, the patient was admitted to the intensive care unit with marked respiratory acidosis, respiratory failure and alterations in consciousness. At the follow-up, the patient was not diagnosed with a systematic disorder. Rather, the patient's historical clinical findings suggested a metabolic disorder. Finally, the patient was diagnosed with biotinidase deficiency.

Conclusion: Even though biotinidase deficiency is not frequently seen in the intensive care unit, metabolic syndromes such as biotinidase deficiency should be considered. Patients should be evaluated holistically with attention to medical history, family history and clinical findings.

Keywords: Biotinidase deficiency, respiratory failure, acidosis, respiratory

Biotin is a cofactor of the carboxylase enzymes that functions in fatty acid synthesis and amino acid catabolism. The biotinidase enzyme regulates the recycling of biotin. Biotinidase deficiency (BD) is a rare inherited autosomal recessive disorder that is treatable during childhood (1). The major symptoms of BD are hypotonia, respiratory abnormalities, ataxia, vision and hearing loss, skin lesions, alopecia, developmental delays, metabolic acidosis and hyperammonemia (2). The worldwide incidence of this disease is 1 per 60,000 births (3).

Although BD is a childhood disorder, there are adult cases that are asymptomatic and diagnosed through family screening (4). We present a patient with pneumonia and respiratory acidosis, who had a history of metabolic alkalosis that had not previously been associated with any systemic disorder, who was finally diagnosed with BD.

CASE PRESENTATION

A 30-year-old woman was admitted to the emergency department with respiratory failure that had persisted for several days. After the deterioration of her general condition, the patient was admitted to the intensive care unit (ICU) with marked respiratory failure and acidosis. Written informed consent was obtained from the patient's relatives.

On clinical examination, the patient was unconscious, and her Glasgow coma score was assessed as "7". Her pupils were bilaterally isochoric and mydriatic. Light reflexes were positive. Kernig/Brudzinski sign and nuchal rigidity were negative. She had vision loss and sensorineural hearing loss. On auscultation, rough rhonchi in the right middle area of the lung were noted. The patient's heart rate was 120/min and blood pressure was 90/60 mmHg. On an inspired oxygen concentra-

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tion of 30%, the blood gas analysis showed pH of 7.12, $paCO_2$ of 113 mmHg, PaO_2 of 78 mmHg, BE of 7.0 mmol/L, HCO_3^- of 36.3 mmol/L, Cl^- of 104 mmol/L and lactate of 5 mmol/L. On serum analysis, hemoglobin was 12.3 gr/dl, platelets were $206.10^3/mm^3$, creatinine was 0.4 mg/dl, Na^+ was 143 mmol/L, K^+ was 4.4 mmol/L, C-reactive protein was 127mg/L and sedimentation rate was 110 mm/h. The patient's initial APACHE II and SOFA in the ICU were 18 and 3, respectively.

The patient was intubated because of hypercapnia and ventilated with pressure-control ventilation. She had a fever and purulent tracheal secretions. Tracheal, urine and blood cultures were taken, and empiric antibiotic therapy was started. A detailed history taken from her family revealed that she also had weakness, gait difficulty, alopecia that had been present since birth and progressive vision and hearing loss. The patient's sister had died at the age of 30 years with similar progressive neurologic and respiratory failure, as well as vision and hearing loss. Tests performed on the patient for hyperventilation, excessive sweating, and tachycardia, such as thyroid function tests, respiratory function tests, rhythm Holter and urine vanyl mandelic acid levels, were normal. Two months earlier, she had been admitted to another ICU with tachypnea and hyperventilation. Previous arterial blood gas analysis had revealed respiratory alkalosis with a pH of 7.60, $paCO_2$ of 12 mmHg, PaO_2 of 103 mmHg, lactate of 2.6 mmol/L, BE of 9.4 mmol/L, HCO_3^- of 12.3 mmol/L and Cl^- of 100 mmol/L.

While the patient was being monitored in our ICU, we found no systemic disorder. We considered that the patient might have a metabolic syndrome due to the clinical findings; therefore, we consulted with the department of genetic and metabolic disorders. The homocysteine level and organic acid level in the urine were within normal ranges, as were ammonia and creatine kinase levels in the serum. The measured biotinidase enzyme activity and the biotinidase level were 1.47% (normal range 8%-10%) and 0.13 mU/mL (normal range 6.9–9.45 mU/mL), respectively. These values were extremely low compared to the normal ranges. Based on these results, the patient was diagnosed with BD.

While we were administering the biotin replacement (Medobiotin tablets, Medopharm Arzneimittel GmbH; Ehrenkirchen, Germany) at 10 mg per day with carnitine (L-carnitine, Hi Tech Pharmacal Co. Inc; Amityville, NY, USA), we simultaneously attempted to wean the patient from the mechanical ventilator. However, these attempts failed because she was unable to throw her secretions, probably due to respiratory muscle failure, even though her serum phosphorus level (2.3 mmol/L) was normal. The patient was tracheostomized on the 15^{th} day of follow-up to simplify the weaning process and to shorten the orotracheal intubation period. During this period, the patient's hemodynamic and blood gas analyses improved, and she was successfully weaned from mechanical ventilation (Table 1). The patient began oral feeding, followed by spontaneous breathing, and within three days she was transferred to the ward upon becoming hemodynamically and clinically stable.

DISCUSSION

The prevalence of BD in Turkey is 1/14.800, which is 8 times higher than the world average (3). This is a childhood disorder, but it can appear in adulthood as partial or profound BD associated with low enzyme levels. The clinical findings are divided in five categories: neurologic (hypotonia, seizures, ataxia and developmental delays), sensory (vision and hearing loss, optic atrophy and sensorineural problems), metabolic (acidosis and organic aciduria), respiratory (laryngeal stridor, tachypneic and apneic episodes), and dermatologic (alopecia and eczematous skin lesions). Patients usually present with one or more signs and symptoms, depending on the severity of the disease (4). Our patient was an adult whose problems had continued since childhood, with fluctuating neurologic findings and alopecia. Baykal et al. (3) studied the families of children with BD and found that asymptomatic individuals had partial BD. It is important to identify these asymptomatic patients in order to inform them about the risks and the nature of this disease, as it is possible that these individuals could become symptomatic if exposed to stress, such as an infection. Epigenetic factors and dietary differences in biotin intake protect some enzyme-deficient individuals from developing symptoms (5). Individuals with profound

TABLE 1. Serum findings before and after ICU admission.

	Before ICU admission	After ICU admission
pH	7.12	7.35
PaO2	78 mmHg	89 mmHg
PaCO2	113 mmHg	45 mmHg
Lactate	5 mmol/L	3 mmol/L
BE	7.0 mmol/L	6 mmol/L
Na+	143 mmol/L	140 mmol/L
K+	4.4 mmol/L	4 mmol/L
Ammonia	78 mg/L	35 mg/L
Creatinine	0.4 mg/dL	0.6 mg/dL
CRP	127 mg/dL	34 mg/dL

pH: log of serum H+; PaO^2: partial oxygen pressure; $PaCO^2$: partial carbon dioxide pressure; BE: base excess; Na+: sodium in concentration; K+: potassium ion concentration; CRP: C-reactive protein; ICU: intensive care unit

BD often become symptomatic if untreated, but certain individuals with profound BD remain asymptomatic (3). The biotinidase enzyme activity in partial BD is 1–10%; this measure drops below 1% in profound BD (6). This value was 1.7% in our patient, which could be accepted as profound BD. The patient's intermittent symptomatic episodes since childhood were also consistent with profound BD. Her recent condition had worsened due to infection and she became symptomatic, finally deteriorating to respiratory failure.

Clinical features such as vomiting, hypotonia and seizures accompanied by metabolic acidosis or mild hyperammonemia are often observed in inherited metabolic diseases (5). Individuals with BD may exhibit clinical features that are misdiagnosed before being correctly identified (7,8). Biotinidase determination in serum/plasma is the best way to diagnose BD. Biotinidase activity is normal in the serum of individuals with holocarboxylase synthetase deficiency, who may have similar symptoms; however, the biotin level is a marker to distinguish BD from other deficiencies. Our patient had low biotin and biotinidase enzyme levels.

Lactic acidosis is likely to be seen in patients with BD. Pyruvate dehydrogenase is an enzyme of the tricarboxylic acid cycle that uses biotin as a cofactor. This enzyme does not function without biotin, so lactate levels increase as a consequence of BD (9). BD is also the major cause of late-onset biotin-responsive multiple carboxylase deficiency. Our patient had mild hyperammonemia with normal liver function tests, which may have been associated with these enzyme defects. Such metabolic and respiratory defects make the diagnosis of this condition quite difficult. BD causes apneic and tachypneic episodes with both acidosis and alkalosis. Patients with BD also have respiratory problems such as hyperventilation, laryngeal stridor and apnea.

In conclusion, although BD is not frequently seen in the ICU, metabolic syndromes such as BD should be considered in ICU patients, who should be evaluated holistically with a family history and clinical findings. When we investigated the literature, we found no adult cases that became symptomatic. Many cases were children or neonates, although BD does not manifest during the neonatal period. The published literature contains one report of a newborn with respiratory distress and tachypnea (10). The present article reports on a rare adult BD case, which we hope will shed light on a different aspect of this disease.

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Informed Consent: Informed consent was obtained from the patient's relatives for this case.

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