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ISOVALERIC ACIDEMIA*

Clinical Presentation of 6 Cases

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A retrospective study is reported on the clinical outcome of six patients with isovaleric acidemia (IVA) diagnosed during the last 20 years at the Metabolic Unit of Hacettepe University Children's Hospital. IVA is only one of many inborn errors of metabolism that may have an acute or a late, intermittent presentation. Generally, the diagnosis cannot be made by clinical or routine clinical chemical investigations, although the odor of "sweaty feet" is a presenting symptom. An unusual urinary odor, which was present in all of our patients, should lead to a thorough screening for organic acidemia at any age. Here, we have reported six patients with IVA. Two pairs were siblings. All, except one patient, had positive family history of sibling deaths and all parents were related. In our series, only two patients presented during the neonatal period and both died during the acute crisis. The other four patients presented after the neonatal period and were categorized as having a chronic intermittent form of IVA. Two cases showed normal development despite repeated metabolic decompensations; one patient was diagnosed during the first attack, but he was mentally and motor retarded. The other one died during the metabolic crisis. The presented cases clearly illustrate that IVA can be managed successfully once the diagnosis is made. But lack of early recognition may lead to severe psychomotor retardation or death. *Key words: isovaleric acidemia, sweaty feet odor.*

Isovaleric acidemia (IVA) is a disorder of leucine catabolism caused by deficient activity of isovaleryl-CoA dehydrogenase with autosomal recessive inheritance[1]. Two clinical forms are distinguished: 1. acute neonatal form, and 2. chronic form with recurrent attacks of severe ketoacidosis.

If untreated, patients may suffer from permanent brain damage or die, but if the condition is managed with a low-leucine diet, L-carnitine and glycine, they may remain clinically well unless challenged by an infection[2].

Here, a retrospective study is reported on the clinical outcome of six patients diagnosed with IVA during the last 20 years in our clinic.

Case Reports

Six patients who have been diagnosed at the Metabolic Unit of Hacettepe University Children's Hospital as having IVA are included in this study. Clinical and laboratory data of the patients were obtained from hospital records. Some clinical details of the cases are given in Table I.

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Table I: Some Clinical Characteristics of Cases with Isovaleric Acidemia

Patient	Age Sex	Consan-guinity	Family History	Presenting Symptoms	Clinical, Laboratory Findings	Treatment	Outcome
1-(MŞ)*	2½ years male	+	–	vomiting, lethargy, irritability	lethargy, "cheesy" odor, metabolic acidosis	IV fluid, $NaHCO_3$	died
2-(NŞ)*	13 months female	+	+	vomiting, lethargy, fever	lethargy, "sweaty feet" odor, ketonuria, metabolic acidosis	IV fluid, $NaHCO_3$, carnitine, low protein diet	alive
3-(ZŞ)**	7 days female	+	+	poor sucking, lethargy	tachypnea, coma, "rancid" odor, metabolic acidosis, anemia, thrombo-cytopenia	IV fluid, $NaHCO_3$, antibiotic	died
4-(HŞ)**	4 years male	+	+	lethargy, develop-mental delay	lethargy, "sweaty feet" odor, metabolic acidosis	IV fluid, $NaHCO_3$, carnitine	alive, mental-motor retarded
5-Baby Ç	5 days male	+	+	poor feeding	hypotonia, dehydration, lethargy, irregular respiration, "sweaty feet" odor, metabolic acidosis, neutropenia	IV fluid, $NaHCO_3$, antibiotic	died
6-(TK)	5½ years male	+	–	pallor, dark urine, chickenpox, altered mental status	deep breathing, pale and subicteric skin, lethargy, chickenpox, hemolytic anemia, metabolic acidosis	IV fluid, $NaHCO_3$, blood transfusion, carnitine, glycine	alive

* siblings.
** siblings.

Case 1 (MŞ): The two-and-one-half-year-old boy was admitted to the hospital with a short history of vomiting, and became rapidly unwell with lethargy and irritability. He was the product of an uncomplicated term delivery born to third degree relative parents. Two older female siblings were well. His developmental milestones were reported to be normal by the parents.

On admission, he was lethargic and acidotic, and a "cheesy" smell was noticed on his breath. He rapidly lapsed into coma. He was found to have a metabolic acidosis (pH: 6.99, HCO_3: 4.66 mmol/L). His plasma electrolytes and blood glucose were normal as were his hemoglobin and white cell count. He was treated with intravenous fluids and sodium bicarbonate, but his condition did not improve over the next hours and he died. Organic acid analysis of his urine by gas chromatography-mass spectrometry (GC-MS) led to the diagnosis of IVA.

Case 2 (NŞ): A thirteen-month-old girl was well until she presented to a local hospital with a 48-hour history of vomiting, lethargy and fever. The child was treated with intravenous fluid and bicarbonate. She was transferred to our hospital. She was the sibling of Case 1. Our findings on physical examination were limited to a slight lethargy. An odor of "sweaty feet" was noticed on her urine. The patient required 1 mg/kg/day of sodium bicarbonate to maintain a serum bicarbonate of 22 mEq/L for 48 hours. She was then discharged on a low protein diet and carnitine.

Fifteen days following discharge, she was rehospitalized because of urinary infection, vomiting, dehydration and slight metabolic acidosis. Serum concentration of sodium was 142 mEq/L, potassium 5.8 mEq/L, chloride 108 mEq/L. Urine ketone was 4+. She was treated with intravenous bicarbonate and antibiotics. The urinary organic acid pattern showed the typical pattern for IVA with increased excretion of isovalerylglycine, isovaleric acid, β-OH butyrate, acetoacetate and lactate.

Two more admissions for acute infectious laryngitis and viral hepatitis were necessary at the ages of two and four years. The patient is now 10 years old: her growth and neurological evaluatilon are normal, and her school performance is good. She is still on a low-protein diet and is taking 100 mg/kg/day carnitine orally.

Case 3 (ZŞ): The patient, a girl, was the seventh child of parents who were second cousins; four of her siblings had died between one and nine months of age. The infant was well at birth, but began to refuse feeding and started vomiting on the seventh day of life. When she was hospitalized at a local hospital, a presumptive diagnosis of sepsis neonatorum was made and laboratory investigations revealed acidosis. Parenteral broad spectrum antibiotics and sodium bicarbonate solutions were given. Her condition improved and she was discharged on a high protein-high caloric diet on the 17th day of admission. She

was brought to our hospital the next day with lethargy and poor sucking. She was noted to be tachypneic and to have gastrointestinal bleeding. A rancid odor was noticed on her body but this clue could not be identified. Her hemoglobin was 9.4 g/dl, and white-cell count 16.000/mm^3. Thrombocytopenia was also noticed on her blood smear. The serum electrolytes were normal, but carbondioxide content was low (6.4 mEq/L). The initial clinical impression was sepsis. Antibiotic therapy was started, and intravenous bicarbonate was given. However, the patient continued to deteriorate, and profound coma developed within 12 hours. She died soon thereafter.

The specific diagnosis of IVA was suggested after her sibling (Case 4) was diagnosed as having IVA.

Case 4 (HŞ): A four-year-old boy was brought to hospital with a complaint of lethargy. He was the 10^{th} child of consanguineous healthy parents. The pregnancy was uneventful and the infant was normal at birth. Developmental delay was noticed by his parents. His family history was suggestive for a metabolic disease: Five of his siblings had all died in the first year of life with vomiting, poor sucking and altered consciousness. On admission, physical examination revealed a well-grown (weight 18.5 kg, 50^{th}-75^{th} percentile; height 109 cm, 90^{th}-97^{th} percentile) and slightly encephalopathic child. He was responsive to verbal stimuli. The blood pH was 7.2, HCO_3: 12.1 mmol/L. IVA was provisionally diagnosed because of the characteristic odor, and intravenous infusion of sodium bicarbonate and carnitine was started. Organic acid analysis showed increased isovaleric acid, isovalerylglycine and other conjugates, confirming the diagnosis.

The child was discharged on reduced protein intake supplemented with glycine and carnitine.

When he presented with generalized seizures at six-and-one-half years of age, EEG showed diffuse abnormalities, and antiepileptic therapy was started. He is now seven years old-his developmental assessment showed delays in most areas but his physical examination gave normal results otherwise.

Case 5 (Baby Ç): A five-day-old male infant was the third child of consanguineous healthy parents and the product of a twin pregnancy. The first child of the couple had been normal at birth, but had become lethargic on the sixth day of life and died. The second pregnancy was uneventful and the babies were born by cesarean section delivery. They were breastfed and seemed well until the third postnatal day when they presented with seizures and were noted to feed poorly and to be tachypneic. One twin died on the fifth day. Baby Ç was transferred to the neonatal intensive care unit. On admission, he was hypotonic, hypothermic (rectal temperature 35.5 °C), dehydrated and lethargic with signs of respiratory distress. Newborn reflexes were absent. The blood

glucose concentration was 47 mg/dl, venous blood pH: 7.1, and HCO_3: 12.8 mmol/L. Hemoglobin was 20.4 g/dl and the white cell count was low (1,600 mm^3). Urinalysis revealed a 2+ test for protein and a negative test for ketones. The first clinical impression was sepsis neonatorum. Intravenous glucose, sodium bicarbonate and antibiotic therapy were started. The patient's condition worsened within 12 hours and "sweaty feet" odor was noticed on the urine. The respiratory arrest necessitated artifical ventilation; however, his condition deteriorated rapidly and the baby died on the sixth day of life.

The specific diagnosis was confirmed by urinary organic acid analysis by GC-MS. It showed a typical pattern for IVA.

Case 6 (TK): A five-and-one-half-year-old boy was hospitalized with chickenpox, hemolytic anemia, encephalopathy and metabolic acidosis of unknown origin. He was the full-term product of an uneventful pregnancy and delivery. He had normal developmental milestones. His parents were first degree relatives and his two siblings were healthy. At five months and two, four and five years of age, he had been brought to other hospitals with altered mental status, dark urine and vomiting. On each admission, metabolic acidosis and deep anemia were shown, but their etiology could not be determined and the disease remained undiagnosed. All these conditions had been combined with several infectious diseases. On this admission, the body temperature was high (39.1 °C), and physical examination revealed deep breathing, increased pulse rate, pale and subicteric skin with papules, and early and late vesicles with crusts spread to his face, scalp and trunk. There were vesicles on the oral mucous membrane. He was lethargic and ill-looking but arousable. A "sweaty feet" odor was noticed on his body and urine. The clinical picture during this period was dominated by the following hematological abnormalities: The laboratory findings revealed a severe metabolic acidosis with a base deficit of -15.8 mmol/L (pH: 7.2, HCO_3: 9.6 mmol/L). Urinalysis showed 3+ ketones. The hemoglobin was 6.6 g/dl and the reticulocyte count was 3.2 percent with normal white cell count (6,000/mm^3). The peripheral blood smear revealed macrocytosis and polychromatophilia and few spherocytes and fragmented erythrocytes. His blood samples were taken and thereafter transfusions of packed red cells were given. The first impression was an underlying metabolic disease and his blood ammonia, lactate and pyruvate levels were determined. They were within normal limits; however, his plasma amino acid analysis revealed high leucine and glycine levels. The lethargy and acidosis resolved with continuous administration of intravenous fluids of dextrose and bicarbonate. He was noted to be aroused more easily by the second day of therapy and was alert by the third day.

The blood smear findings, the elevated reticulocyte count and elevation of the unconjugated bilirubin level were the overt features of a hemolytic anemia. The plasma hemoglobin concentration was increased; serum haptoglobin was absent.

The osmotic fragility studies and autohemolysis were normal. The hemoglobin electrophoresis did not demonstrate any pathologic pattern. Direct and indirect Coombs' tests were negative. The bone marrow was markedly hyperplastic and showed erythroid predominance. The acid serum (Ham) and sucrose lysis tests were repeated twice but gave negative results.

The diagnosis of IVA was confirmed by demonstrating markedly increased concentrations of isovalerylglycine, 3-OH isovaleric acid and free isovaleric acid in the urine by GC-MS. The patient was discharged on a low-protein diet, and carnitine was prescribed (100 mg/kg/day) orally.

At the age of six-and-one-half years, he was hospitalized again with fever, cough, back pain, vomiting and lethargy. He was diagnosed as having empyema, and hematological and metabolic crises. Closed drainage was instituted and he was treated with intravenous antibiotics, bicarbonate and carnitine infusions. Glycine was added to the therapy and repeated blood transfusions were required. The clinical response was good. The patient was discharged on the 15th day of admission with a low-protein diet, supplemental glycine and carnitine.

He is now 12 years old, and his physical growth and school performance are good. He has not experienced any metabolic decompensation or hemolytic crisis for the last five and one half years.

Discussion

Isovaleryl-CoA dehydrogenase catalyzes the conversion of isovaleryl-CoA to 3-methylcrotonyl-CoA and enzyme deficiency results in toxic accumulation of isovaleric acid and other related organic acids. The disease is characterized by the excretion of isovalerylglycine and 3-hydroxyisovaleric acid (which give the name of disease) and the typical urine odor. Two forms of clinical presentation are common: 1. Acute neonatal form or neonatal onset form occurs within two weeks of birth. Initial symptoms include vomiting, dehydration, listlessness and acidosis[3]. 2. Chronic and intermittent form or late onset form is characterized by exacerbations in the first year of life. Attacks occur during periods of stress, such as viral or bacterial infections, or the ingestion of high-protein foods. Patients may present with vomiting, lethargy progressing to coma, metabolic acidosis characterized by an elevated anionic gap and ketonuria with a distinctive "sweaty feet" odor[4].

Here, we have reported six patients with IVA. Two pairs were siblings (Cases 1-2 and Cases 3-4). All, except for Cases 1 and 6, had positive family history of sibling deaths and all parents were related.

In our series, only two patients, Cases 3 and 5, presented during the neonatal period. In the neonatal form of IVA, affected patients are usually seen during the first two weeks of life with a syndrome of poor sucking, vomiting, lethargy

progressing to coma and ketoacidosis. However, it is known that the neonate has a limited repertoire of responses to severe overwhelming illness and thus the major clinical signs and symptoms are non-specific. As a result, many neonates with metabolic disease succumb without having received a specific diagnosis and with their clinical picture having been attributed to other common conditions such as sepsis[5]. In this group, two neonates were considered as having sepsis despite positive sibling histories and the strange odor detected on their bodies. Even the specific diagnosis of Case 3 was suggested only after her sibling (Case 4) was diagnosed as having IVA many years later. Case 5 was one of a set of twins; the other child having died with the same clinical picture. It could be considered that he, too may have had IVA. The morbidity and mortality of IVA in the neonatal period is high[3]. In our series, these two patients died during the acute crisis.

Four other patients presented after the neonatal period, and were categorized as having the chronic intermittent form of IVA. The age range of presentation was broad: 13 months to four years. Case 6 was diagnosed as having IVA at five-and-one-half years of age, but he had first presented at five months of age. It is interesting that the disease presented in different phenotypes in the same family: Cases 3 and 4 were siblings. One of them presented during the neonatal period, but in the other, developmental delay was the unique feature of IVA until four years of age, when he developed an acute attack.

Recurrent attacks of coma and lethargy are the main presentations of the chronic intermittent form of organic acidemias. The most frequent variety of coma is that presenting with ketoacidosis, although in rare cases, ketosis may be absent. In our series, lethargy and vomiting were the major symptoms in all cases; only Case 1 sank into coma despite supportive measures. The others were responsive to supportive therapy.

Hypoglycemia is rare in patients with IVA. All patients in this group were normoglycemic during acute metabolic crises.

The typical odor of IVA, which is the excellent key to the diagnosis, was noticed in all cases, although it was identified only in four cases. In Cases 1 and 3, a "cheesy" or "rancid" odor was noticed, but this important clue could not be appraised.

The clinical syndrome of IVA is dominated by the neurological findings, but the severe hematological abnormalities are also frequently described in the disease. Inhibition of hematopoietic cellular metabolism by toxic derivative compounds interferes with maturation of bone marrow and is responsible for the hematological findings of IVA[6]. These hematological findings are concomitant with ketoacidosis, but sometimes they are the presenting symptoms. Pancytopenia is a characteristic feature of this syndrome. Neutropenia is regularly observed in both neonate and late onset forms of organic acidurias. Thrombocytopenia occurs only in infancy and anemia only in the neonatal period[7].

In this series, the hematological findings were observed in only three patients. In Case 3 the hemoglobin was low and thrombocytopenia was noticed on the blood smear, but the white cell count was high. In Case 5, neutropenia (1,600/mm^3) was noted, but the hemoglobin and thrombocyte counts were normal. All these findings were attributed to sepsis neonatorum but in retrospect they were compatible with the diagnosis of IVA. It could be said that they were the contributory factors to the cause of death in these neonates.

The hematological abnormalities as described above are reported in the literature, but there has been no report about hemolytic anemia in IVA. In Case 6, at least six hematological and metabolic crises triggered by infectious diseases were noted. Despite many efforts, no explanation could be found for the cause of hemolysis. However, it could be said that the hemolytic crises were precipitated by infection which triggered metabolic crises or acidosis. With appropriate management, the hemolytic crisis has not recurred in this patient.

Cases 2 and 6 showed normal development despite repeated metabolic decompensations. Case 4 was diagnosed during the first attack, but the was mentally and motor retarded. Generally, a normal mental development or a mild mental retardation have been described in this disease. The pyschomotor development of children with IVA may be completely normal[8]. This point draws more attention to the potentially lethal hematological abnormalities. Patients with this controllable disease can be lost because of hemolytic disease, hemorrhage or neutropenic sepsis.

The presented cases clearly illustrate that IVA can be managed successfully once the correct diagnosis is made. Its diagnosis requires a high index of suspicion in neonates presenting with a clinical picture resembling that of sepsis and in older children presenting with repeated acidotic attacks, lethargy and certain hemotological abnormalities in the presence of parental consanguinity and/or positive history for sibling deaths. The unusual urinary odor which was present in all of our patients should have led to a through screening for organic acidemias and thus to the diagnosis of IVA.

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