The Turkish Journal of Pediatrics 1997; 39: 379-385

ACUTE PANCREATITIS IN A PATIENT WITH GLUTARIC ACIDEMIA TYPE II*

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SUMMARY: Coşkun T, Göğüş S, Akçören Z, Tokatlı A, Özalp İ. (Nutrition-Metabolism and Pathology Units, Department of Pediatrics, Hacettepe University Faculty of Medicine, Hacettepe-Ankara, Turkey). Acute pancreatitis in a patient with glutaric acidemia type II. Turk J Pediatr 1997; 39: 379-385.

We describe a two-year-old girl who presented with coma following an upper respiratory tract infection. Nonketotic hypoglycemia, metabolic acidosis and mild hyperammonemia were detected. The urinary organic acid profile was consistent with glutaric aciduria type II. Pancreatitis was diagnosed at autopsy. Although pancreatitis has been described in a number of inborn errors of metabolism including organic acidemias, to the best of our knowledge this is the first report of acute pancreatitis occurring in glutaric acidemia type II. It was stressed, therefore, that this complication should be searched for in organic aciduria patients, and the measurement of plasma amylase and lipase levels should be added to the battery of laboratory investigations in such cases. *Key words: glutaric acidemia type II, pancreatitis.*

The number of reports on the occurrence of acute and chronic pancreatitis in patients with inborn errors of metabolism has been increasing in recent years. Among the metabolic diseases reported with accompanying pancreatitis are maple syrup urine disease[1], isovaleric acidemia[1], methylmalonic acidemia[1], propionic acidemia[2], 3-OH-3-methyl glutaric aciduria[3], homocystinuria[4], Pearson syndrome[5], cytochrome c oxidase deficiency[6], glycogen storage disease type I[7,8] and carnitine palmitoyltransferase II deficiency[9]. Glutaric acidemia type I was added to the list most recently[10]. To our knowledge, acute pancreatitis in glutaric acidemia type II or multiple acyl CoA dehydrogenation deficiency has not previously been described. In this report we describe acute pancreatitis occurring in a two-year-old girl with glutaric aciduria type II.

Case Report

The patient, a two-year-old female, was admitted to Hacettepe University İhsan Doğramacı Children's Hospital in a coma following a brief period of seizure. She had an upper respiratory tract infection characterized by fever, nasal discharge

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and cough that started two days prior to her admission, and was hospitalized with the presumptive diagnosis of Reye's syndrome or encephalitis. Her parents were first cousins, and two siblings were healthy. She had reportedly been hospitalized at a local hospital for approximately one week with a suspected diagnosis of "aseptic meningitis" when she was six months old.

On physical examination, the patient's general condition was poor and she was unconscious. She had grunting respirations. The body temperature was 36.5 °C, pulse 120, and respirations 28/minute. The liver was palpable four centimeters below the right costal margin. Deep tendon reflexes were found to be slightly increased, and the Babinski sign was positive bilaterally. Her body weight was 15 kg ($> 90^{th}$ percentile), length 85 cm ($< 50^{th}$ percentile), and head circumference 46 cm ($< 10^{th}$ percentile).

Laboratory values included Hb: 10.4 g/dl, Hct: 30.7%, WBC: 8.700/mm^3 with 90% polymorphonuclear leukocytes, 8% lymphocytes and 2% band forms. Urinalysis was normal. Serum electrolytes were sodium: 135 mEq/L, potassium: 6.2 mEq/L, chloride: 87 mEq/L, and HCO_3^-: 11 mEq/L. Serum glucose was 11 mg/dl, BUN: 24 mg/dl, calcium: 9.5 mg/dl, phosphorus: 7 mg/dl, SGOT: 702 U/L, SGPT: 401 U/L, alkaline phosphatase: 202 U/L, total bilirubin: 0.6 mg/dl (conjugated fraction: 0.4 mg/dl), total protein: 7.1 g/dl, albumin 4.7 g/dl, creatine phosphokinase: 3,829 U/L, and arterial pH: 7.41. The blood ammonia level was 180 µg/dl (normal: 20-120 µg/dl), lactate: 27.3 mg/dl (normal: 10-14 mg/dl), and pyruvate: 2.8 mg/dl (normal: 0.5-1.0 mg/dl). The prothrombin and partial thromboplastin times were 15.5 and 30 seconds, respectively. EEG revealed a widespread suppression of the cerebral bioelectric activity. Cranial computed tomography demonstrated brain edema. A fatty liver was found on abdominal ultrasonography. Gas chromatographic-mass spectrometric analysis of urine was consistent with glutaric aciduria type II.

Despite mechanical ventilation and parenteral administration of dextrose, fluids, fresh frozen plasma, bicarbonate, vitamin K, antibiotics and acyclovir, the patient died on the sixth day of admission.

Autopsy revealed a pale liver weighing 540 g (normal: 430 g). The brain was edematous with a weight of 1125 g (normal: 1012 g). The pancreas (weight: 48 g, normal: 19.9 g) was also edematous and had hemorrhagic areas. No congenital anomaly was detected.

Fatty infiltration of the liver with both small- and large-sized lipid vacuoles was found on microscopic examination (Fig. 1). Frozen sections of the liver showed diffuse staining with oil red O. Microscopic examination of the pancreas disclosed an acute, diffuse and hemorrhagic pancreatitis and necrosis of the peripancreatic fat tissue (Fig. 2). Sections of the brain revealed edema and anoxic changes. There was

necrosis of the granular layer of the cerebellum. Spongiosis was detected between the gray and white matter in many sections of the cerebral cortex (Fig. 3). Bronchopneumonia and intraalveolar hemorrhage were present in the lungs.

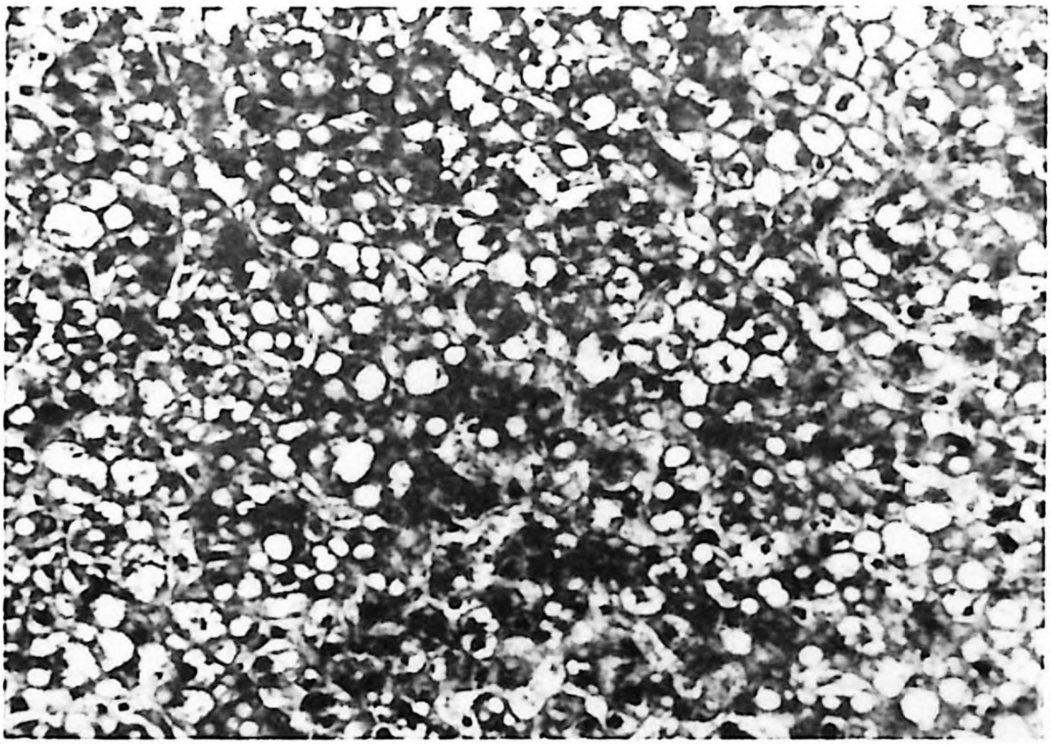

Fig. 1: Small and large lipid vacuoles in the liver. H-E, x66.

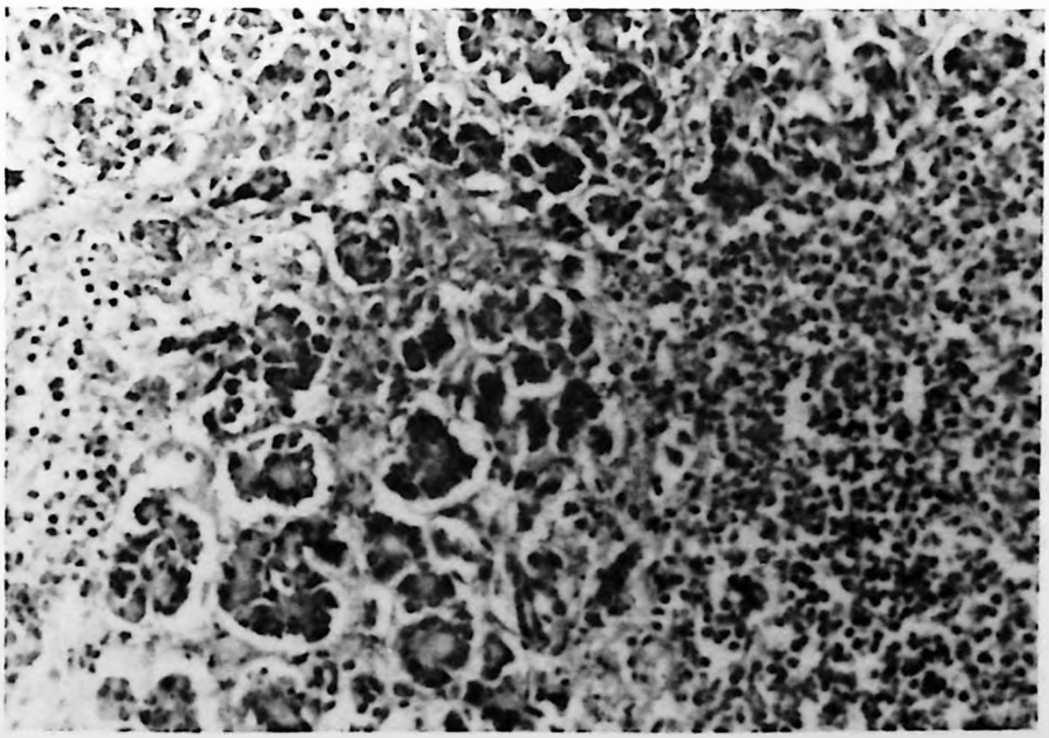

Fig. 2: Necrosis and inflammatory reaction in the pancreas. H-E, x66.

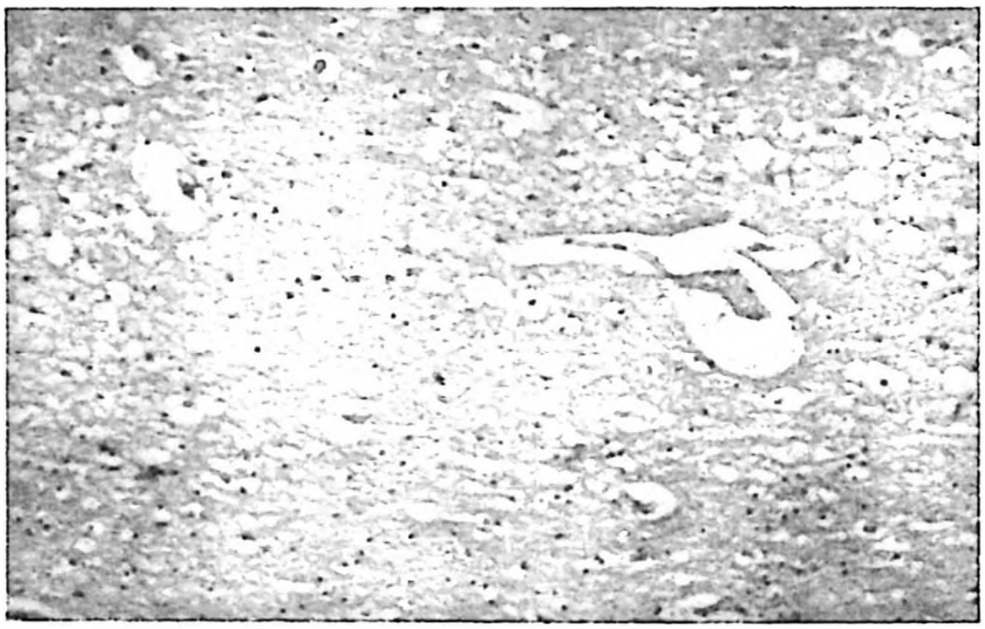

Fig. 3: Spongiosis between gray and white matter of the cerebral cortex. H-E, x33.

Discussion

Glutaric acidemia type II is an inborn error characterized by hypoketotic or nonketotic hypoglycemia, metabolic acidosis, hyperammonemia and organic aciduria. The underlying metabolic defect that causes the disease is a deficiency of either electron transport flavoprotein (ETF) or electron transport flavoprotein oxoreductase (ETF-QO). The mode of inheritance is autosomal-recessive. The disease is heterogenous both clinically and biochemically. Some affected infants present with life-threatening illnesses in the neonatal period, with or without congenital anomalies, while others may have the mild- or late-onset form and become symptomatic later in life[11]. The clinical picture of glutaric acidemia type II, particularly that of the neonatal form, may well mimic Reye's syndrome[12]. Many affected patients have facial dysmorphism, abnormalities of the external genitalia, polycystic kidneys with or without dysplastic changes, and symmetrical warty dysplasia of the cerebral cortex[11, 13-16]. Our patient, presenting with metabolic acidosis, nonketotic hypoglycemia, slightly increased blood ammonia and hepatomegaly at two years of age, belongs to the second group. Although no further information was available, we assumed that the episode experienced at six months by our patient and diagnosed as "aseptic meningitis" might well have been a mild attack of the disease. The typical urinary organic acid pattern established the diagnosis of glutaric acidemia type II in the patient.

Organic acidemias account for a considerably large group among the inborn errors of metabolism, and a number of these have been reported to be associated with either acute or chronic pancreatitis[1]. It was found that nine out of 108 children with organic acidemia had pancreatitis in a study covering five institutions, a

finding that gave further support to the hypothesis that the occurrence of pancreatitis in organic acidemias is not fortuitous and points to a causal link[1].

Pancreatitis in glutaric acidemia type I but not type II has previously been reported[10]. To our knowledge, this is the first report of acute pancreatitis in glutaric acidemia type II. Cases reported earlier led the current authors to think that pancreatitis develops in organic acidemias mostly due to impaired metabolism of branched-chain compounds[1]. In fact, several other mechanisms have been hypothesized. These include a direct toxic effect of the accumulated compounds, particularly that of triglycerides on the acinar cell membrane, lack of ATP, excess free-radical formation and deficiencies of carnitine, methionine and antioxidants, and a low-protein high-lipid diet[1, 10].

Acute pancreatitis is rather uncommon in childhood and difficult to diagnose[1]. Its diagnosis is even more difficult in organic acidemia patients, since the conditions share certain common gastrointestinal manifestations, such as feeding refusal, nausea, vomiting and abdominal pain. Moreover, amylase and lipase determinations are not usually included in the battery of laboratory investigations done during acute decompensation in such disorders. This was the case in our patient, and the diagnosis of pancreatitis was made only at autopsy.

A literature search disclosed postmortem examinations of fewer than 30 cases with glutaric acidemia type II[13-15, 17, 18]. Similar to that found in our case, fatty degeneration of the liver parenchymal cells characterized by small-, medium- and large-sized droplets were the most common findings in all the reported glutaric acidemia type II cases to date. These fatty changes in the liver differed from those in Reye's syndrome[13, 15]. Hypoplasia of the ducts and ductules was detected in two cases[16]. Fatty degeneration of the renal tubular epithelium and myocardium has also been reported in glutaric acidemia type II[11-16, 18]. Oil red O stain was not positive in the frozen sections of the formalin-fixed tissues of the kidneys and myocardium in our case. Neuropathologic findings described in several previously reported cases included edema, warty dysplasia, microgyria, Alzheimer type II changes, disordered neuronal migration, hydrocephalus and several other nonspecific changes. Spongiosis of the cerebrum has not previously been described. Only Kamiya et al.[15] mentioned spongioform changes in the gray matter of the spinal cord in their report and hypothesized that these changes might be secondary to hypoxia, hypoglycemia and severe acidosis. The above-mentioned factors may have played a role in our case as well.

Whatever the underlying mechanism, our case when considered together with the lengthening list of previously reported cases points to a causal relationship between organic acidemias and pancreatitis rather than the association of these two being mere chance. Physicians caring for patients with organic acidemias,

particularly those resembling the clinical picture of Reye's syndrome, should be aware of this possibility. Only awareness of this possibility can lead to the diagnosis of pancreatitis in patients with organic acidemias during acute decompensation, or the diagnosis of pancreatitis in the absence of a known cause may lead to the diagnosis of an inborn error of metabolism.

Acknowledgement

We thank Dr. J.G.M. Huijmans, Department of Clinical Genetics, Erasmus University, Rotterdam, The Netherlands, for GC-MS analysis of the patient's urine sample.

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