# NEUROLOGICAL CRISIS MIMICKING ACUTE PANCREATITIS IN TYROSINEMIA TYPE I*

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**SUMMARY: Kalkanoğlu HS, Coşkun T. (Nutrition and Metabolism Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Neurological crisis mimicking acute pancreatitis in tyrosinemia type I. Turk J Pediatr 1999; 41: 501-504.**

**Hereditary tyrosinemia results from an inborn error in the final step of tyrosine metabolism. Neurological manifestations have been reported in nearly half of patients during illness to have characteristics of altered consciousness, weakness, anorexia, vomiting, and pain in the extremities and abdomen. His physical findings and laboratory results pointed out acute pancreatitis. There have been some reports of acute and chronic pancreatitis in patients with metabolic diseases; however, this is the first case with tyrosinemia type I who exhibited clinical and biochemical findings of acute pancreatitis during neurological crisis. The presented case suggests the possibility that the pancreas is affected in neurological crisis. The determination of amylase concentration both in serum and urine samples of further cases will clarify the association between pancreatitis and neurological crisis.** *Key words: tyrosinemia type I, neurological crisis, acute pancreatitis.*

Hereditary tyrosinemia (tyrosinemia type I) is an autosomal recessive disorder caused by a defect of the final enzyme in tyrosine metabolism[1-2]. Affected individuals manifest severe liver disease, a reversible renal Fanconi syndrome, hepatocellular carcinoma, porphyria-like abdominal crisis and frequent neurological manifestations. A syndrome of acute neurological crisis which has striking similarity to the acute porphyrias is seen in as many as 40 percent of the children with this disorder[3]. We describe severe neurological crises associated with extremely high serum and urine amylase concentration as in acute pancreatitis in a child with tyrosinemia type I.

## Case Report

This case was first referred to Hacettepe University Children's Hospital with marked growth retardation, wasting, pathologic fractures at the lower extremities, and hypophosphatemic rickets at the age of three years. The laboratory analyses revealed the presence of renal Fanconi syndrome characterized by a generalized aminoaciduria, phosphaturia, bicarbonaturia and glucosuria. The result of urinary amino acid analysis and serum amino acid quantitation showed an increased

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level of tyrosine. Fumarylacetoacetase activity was found to be low in cultured skin fibroblasts, consistent with the diagnosis of hereditary tyrosinemia type I.

The treatment consisted of continuous supplementation of vitamin D and an oral phosphate for the rickets and of sodium-potassium citrate solution for the acidosis and hypokalemia. A low-tyrosine and phenylalanine diet was used as well.

When he was 16 years old, he was hospitalized for an illness characterized by extreme weakness, anorexia, vomiting and pain in the extremities and in the abdomen. On physical examination, the patient's height was 130 cm and weight 23 kg, which were below the fifth percentile, and his blood pressure was 150/110 mmHg. He had generalized abdominal tenderness without rebound tenderness and tenderness in the legs and arms. He was unable to walk and had generalized hyperreflexia. Neurological findings included delirium and altered consciousness such as somnolence and stupor. He also had disorientation as well as visual, auditory and olfactory hallucinations.

Laboratory data revealed normal serum electrolyte values with the exception of severe hypokalemia. Serum calcium and phosphate levels were low. Serum bicarbonate level was 12.2 mmol/L. Serum transaminases levels were slightly elevated and amylase concentration was 445 U/L and 635 U/L on two consecutive measurements (normal 50-180 U/L). Urinary amylase level of 507 U/L led to amylase clearance which was 6.6 percent. Urinary porphobilinogen was 1.3 µg/ml (normal ≤ 1), coproporphyrin 36.7 mg/ml (normal ≤ 60), uroporphyrin 7.8 µg/L (normal ≤ 10), delta aminolevulinic acid 5.2 µg/L (normal ≤ 4.5), serum coproporphyrin 48.2 µg/dl (normal ≤ 4.5), blood ammonia 125 µg/dl (normal ≤ 120), and prothrombin time was normal.

Urinary and serum amino acid chromatography revealed an increased concentration of tyrosine (serum tyrosine level was 6.8 mg/dl). Abdominal ultrasonography showed an irregular pattern of the liver parenchyma. Alpha fetoprotein was 5.3 ng/dl (normal ≤ 5.9) Electromyography and cranial magnetic resonance imaging were normal and EEG showed no epileptic focus. Plasma renin activity was 16.2 ng/ml/h (normal ≤ 5.7) and urine succinylacetone level was 14 µmol/L.

Initial treatment included intravenous fluids containing bicarbonate and potassium, and oral phosphate supplement. His blood pressure was regulated by a beta-blocker. After starting the 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC) therapy, all his signs and symptoms resolved and he was discharged. The patient continues to use NTBC and anti-hypertensive drugs.

## Discussion

Hereditary tyrosinemia type I is an autosomal recessive disorder of amino acid metabolism caused by a deficiency of fumarylacetoacetate hydrolase, the final

enzyme in the metabolic pathway of tyrosine breakdown. This disorder, with an incidence of 1 in 100,000, leads to liver failure in the first year of life or cirrhosis and hepatocellular carcinoma in the first two decades. Renal tubular dysfunction and neurological crisis may complicate the clinical course[4]. As in the acute porphyrias the episodes of acute neuropathy associated with tyrosinemia are best correlated with ALA excretion and are due to competitive inhibition of ALA dehydrase by succinylacetone, a metabolite of tyrosine degradation[5]. Neurological manifestation of this disorder may include depression, delirium, psychosis, altered consciousness (somnolence to coma), and seizures[6].

Signs and symptoms of acute intermittent porphyria, crises-related weakness, myalgia and abdominal pain and anorexia and elevated urinary excretion of ALA were detected in our patient. Delirium and paranoia manifested later, further deteriorating his neurological state. During this crisis symptoms of abdominal pain, high levels of serum and urine amylase and amylase clearance mimicked acute pancreatitis. In recent years, there have been an increasing number of reports of acute and chronic pancreatitis in patients with inborn errors of metabolism, such as maple syrup urine disease, isovaleric acidemia, methylmalonic acidemia, propionic acidemia, 3-OH-3-methyl glutaric aciduria, homocystinuria, Pearson syndrome, cytochrome c oxidase deficiency, glycogen storage disease type I, carnitine palmitoyltransferase II deficiency and glutaric acidemia types I and II[7-16]. Pancreatitis is relatively rare in childhood and difficult to diagnose. The common signs and symptoms are non-specific, with gastrointestinal manifestations such as anorexia, nausea, vomiting and abdominal pain. Laboratory data is not always useful for the diagnosis, and pathological evaluation of the pancreas may be necessary. In our case, the pathological findings of acute pancreatitis were absent. The symptoms, physical examination and laboratory results pointed out a new neurological crisis, the nature of which has not been encountered or reported before in literature. In this case, the causative factor underlying the development of pancreatitis was obscure. Speculatively, the pathogenesis depends on the direct effect of succinylacetone or the accumulation of the porphyrin metabolites. There is no documentation about any pancreatic involvement in the neurological crisis of patients with type I tyrosinemia.

In conclusion, the presented case highlights the fact that pancreatitis may be a component of neurological crisis in patients with hereditary tyrosinemia type I. Therefore, physicians treating such patients should be aware of this possibility and perform all necessary tests to confirm the diagnosis of pancreatitis. Further reports will clarify whether or not pancreatitis is a component of neurological crisis in tyrosinemia type I patients, particularly in those with severe abdominal pain.

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