Turk J Gastroenterol *2014; 25 (Suppl.-1): 216-9*

A very rare cause of acute pancreatitis: Berardinelli-Seip congenital lipodystrophy

Ali İşlek[1], Ersin Sayar[1], Aygen Yılmaz[1], Özgür Duman[2], Reha Artan[1]
[1]Department of Pediatric Gastroenterology, Akdeniz University Faculty of Medicine, Antalya, Turkey
[2]Department of Pediatric Neurology, Akdeniz University Faculty of Medicine, Antalya, Turkey

ABSTRACT

Pancreatitis is among rare diseases in pediatrics clinics. It is usually presented with a sign of underlying systemic disease. Berardinelli-Seip congenital lipodystrophy (BSCL) is a very rare disease characterized by near absence of adipose tissue resulting in apparent muscle hypertrophy from birth or early infancy associated with severe insulin resistance. Common clinical features are hypertriglyceridemia, acanthosis nigricans, hepatomegaly with or without splenomegaly and high stature. Acromegaloid features, cardiomyopathy and mental retardation can also be present. We describe a 7-year-old Turkish boy with these clinical features of BSCL and presented with acute pancreatitis.

Keywords: Pancreatitis, berardinelli-seip congenital lipodystrophy, childhood

Case Report

INTRODUCTION

Acute pancreatitis is usually a self limited disease characterized by sudden onset abdominal pain, elevated levels of serum and/or urine pancreatic digestive enzymes and radiological changes in pancreas. Although exact prevalence is not clear in children, it is not as common as in adults. Approximately in 25% of children diagnosed as acute pancreatitis, no underlying reason has found. The most common etiologies in acute pancreatitis are usually drugs, trauma, systemic infections and diseases (1). One of very rare reason of acute pancreatitis is congenital generalized lipodystrophy, or Berardinelli-Seip congenital lipodystrophy [OMIM 269700] which is a rare autosomal recessive disorder in which characteristic clinical feature is generalized muscular appearance because of the nearly complete absence of adipose tissue (2). Hypertriglyceridemia, hepatomegaly, acromegaloid features, mental retardation, hypertrichosis, precocious puberty, hypertrophic cardiomyopathy, and insulin-resistant diabetes mellitus may usually accompany to the disease (3). The prevalence of BSCL is estimated as one in every 10 million births (4). We presented 7-year-old Turkish boy diagnosed as BSCL to underline this very rare disease in the differential diagnosis of acute pancreatitis.

CASE PRESENTATION

A 7-year-old boy, the older of two siblings from a consanguineous marriage, presented with abdominal pain, vomiting, abnormal face and body habitus. Since birth, he had extreme lack of body fat and a muscular appearance and his face displayed abnormity. He was a normal full-term baby delivered by normal spontaneous vaginal way, with no prenatal, perinatal, or postnatal complications. Medical history revealed nephrotic syndrome since three years old and frequent abdominal pain and vomiting resolving spontaneously. He did not use any drug for nephrotic syndrome or for any illness in the last two years. There was no family history.

His weight was 30 kg (weight for age: 130%), and height was 134 cm (height for age: 111%). In his physical examination, additionally to generalized loss of subcutaneous fat, prominent veins and musculatures over face and limbs, acromegaloid face with large hands and feet and acanthosis nigricans were detected. Abdomen was distended due to hepatosplenomegaly (Figure 1). The genital examination was normal (bilateral testis volume 3 mL/3 mL). Intelligence and school performance was under the peers. Serum biochemical parameters revealed hyperlipidemia (cholesterol; 182 mg/dL, triglyc-

Address for Correspondence: Aygen Yılmaz, Department of Pediatric Gastroenterology, Akdeniz University Faculty of Medicine, Antalya, Turkey
E-mail: aygen@akdeniz.edu.tr
Received: May 23, 2012 **Accepted:** August 12, 2012
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2014.3667

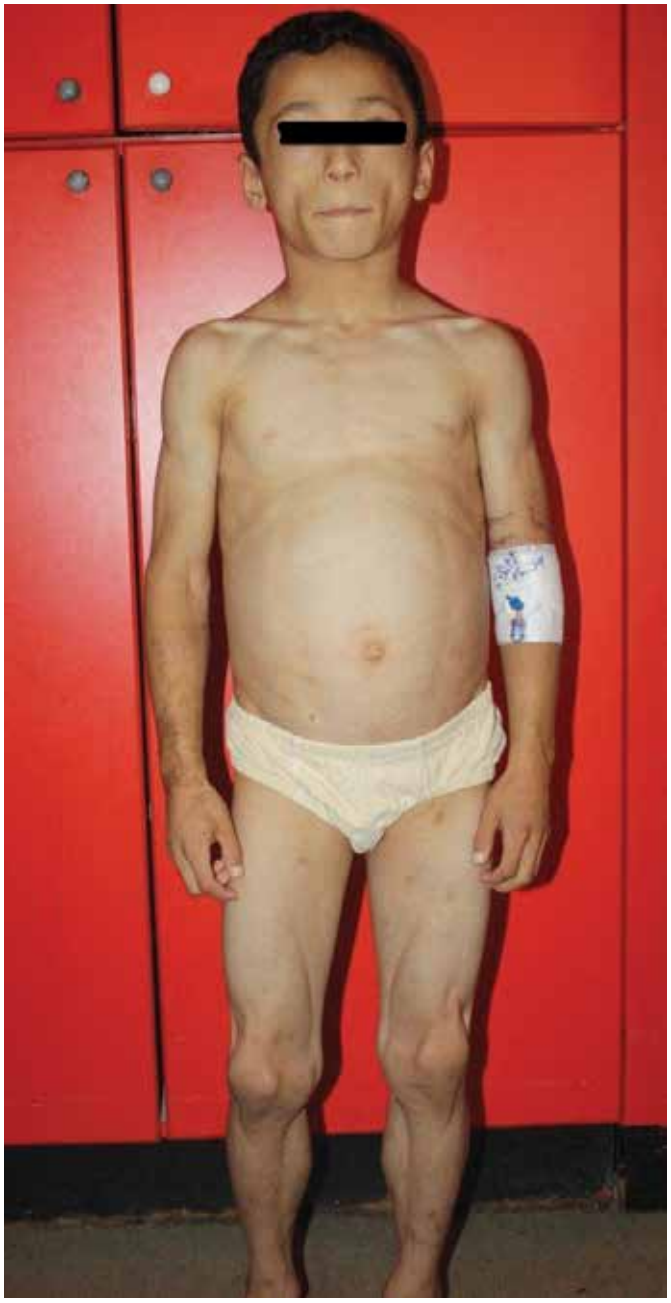

Figure 1. Loss of subcutaneous fat, prominent veins and musculatures over face and limbs, protuberant abdomen.

erides; 912 mg/dL, low density lipoproteins; 137 mg/dL, high density lipoproteins; 27 mg/dL, very low density lipoproteins; 18 mg/dL), hypoalbuminemia (total protein; 8.3 g/dL [6-8.5 g/dL], albumin; 2.1 g/dL [3.5-5.5 g/dL]), elevated aminotransferase levels [(ALT; 104 U/L (0-33 U/L), AST; 132 U/L (0-33 U/L), GGT; 108 U/L (10-61 U/L)] and pancreatitis [pancreatic amylase; 544 U/L (13-53 U/L), lipase; 424 U/L (13-60 U/L)]. Patient's oral intake was restricted and he was treated with intravenous fluid administration. Pancreatic enzymes returned to normal levels. There was severe proteinuria (24 hour urine protein was 149 mg/m^2/h). C_3 and C_4 levels (191 mg/dL and 24 mg/dL respectively), serum glucose level and glucose tolerance curve were all normal but insulin resistance (HOMA-IR: 8.8, serum insulin level was 28.6 µU/mL) was marked. Serum leptin level was < 0.1 ng/mL (normal >0.5 ng/mL). Echocardiography and abdominal ultrasonography revealed hypertrophic cardiomyopathy, hepatosplenomegaly and hepatosteatosis. Renal biopsy could not determine any specific reason of nephrotic syndrome. The genetic tests were performed for BSCL1 (AGPAT2) and BSCL2 (Seipin) genes in "*İnstitut de Pathologie et de Genetique, Gosselies*" but no mutation was identified. Prednisolon and enalapril therapies were used for nephrotic syndrome. Abdominal ultrasonography revealed hepatosplenomegaly and hepatosteatosis. We could not demonstrate the degree of the hepatic steatosis due to parents' refusal of the liver biopsy. In this case saturated fats and long chain triglycerides were replaced with unsaturated fats and MCT. Gemfibrosil for hypertriglyceridemia metformin and ursodeoxycholic acid for insulin resistance and hepatic steatosis were given but patient could not use these drugs because of nausea and allergic reactions. After five months of given a special diet and the treatment of nephrotic syndrome, patient's serum triglyceride concentration and 24 hour urine protein output decreased to 210 mg/dL and 4.5 mg/m^2/h respectively. We thought that previous abdominal pain and vomiting in the patient's history was due pancreatitis. ALT and AST levels decreased to 98 U/L and 102 U/L respectively. Also HOMA-IR value improved 8.8 to 3.4. Up to this time (approximately 20 months), patient did not suffer from pancreatitis.

DISCUSSION

The reason of hospitalization of this patient was pancreatitis. In adults most of cases of acute pancreatitis are associated with alcoholism and biliary tract diseases but the etiology in children is diverse. The most common etiologies are trauma, multisystem diseases, drugs, infections and structural anomalies of the pancreaticobiliary system. Recurrent acute pancreatitis is seen in 10% of children after the initial acute episode. It is more likely in children with congenital structural anomalies, idiopathic and familial causes. Recurrent attacks of acute pancreatitis may cause morbidity and mortality in BSCL. Hypertriglyceridemia seems to the predisposing factor of the pancreatitis in BSCL (3).

Congenital generalized lipodystrophy is a rare autosomal recessive disease. It affects all ethnic groups although many of these cases have involved individuals of Portuguese or Norwegian ancestry. Worldwide, over 500 cases have been reported (3).

Lipoatrophy affecting both trunk and limbs, acromegaloid features including prognatism, salient orbital ridges, enlarged hands and feet, macrogenitosomia, gigantism, muscular hypertrophy and advanced bone age, hepatomegaly, elevated serum concentration of triglycerides and insulin resistance are the major diagnostic criteria for BSCL. The minor criteria include hypertrophic cardiomyopathy, psychomotor or mental retardation, hirsutism, precocious puberty in female and bone

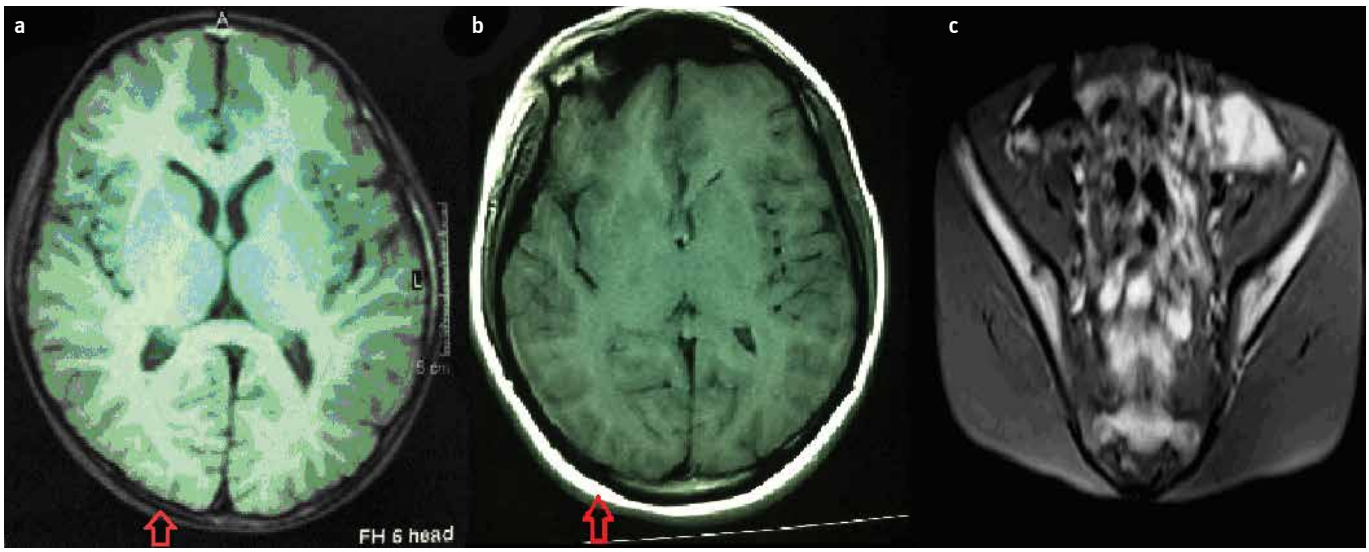

Figure 2. a, b. Loss of subcutaneous adipose tissue is seen in patient's cranial MRI (see arrow) **(a),** a normal cranial MRI with subcutaneous adipose tissue, c. loss of subcutaneous adipose tissue in patient's pelvic region in pelvic MRI **(b).**

cysts. The pathophysiology of lipodystrophies is still unknown. However it is thought to be due to adipocyte deficiency (5). Leptin deficiency, caused by the absence of adipose tissue, could be an important determinant of the metabolic abnormalities. (6).

At least three loci were identified. BSCL1 is less severe phenotype than BSCL2. In type 1, only metabolically active adipose tissue (subcutaneous tissue sites, intraabdominal, intrathoracic sites and bone marrow) is involved. Onset of lipoatrophy may being the second or third decade. No or low frequency of mental retardation. The most severe form is BSCL2 that lipoatrophy is invariably neonatal onset and both metabolically and mechanically active adipose tissues (palms, soles of the extremities, under the scalp, retroorbital and periarticular regions) are involved. A majority of patients have mental retardation. Some rare families appear unlinked to BSCL1 and BSCL2 mutations. The genetic heterogeneity of BSCL, as well as the existence stages of the disease, explains the differences among the main clinical findings of the patients reported previously (7). Our case presented with enlargement of the hands, feet and mandible, loss of adipose tissue, accelerated growth, voracious appetite, increased basal energy expenditure, advanced bone age, acanthosis nigricans, insulin resistance, hypertriglyceridemia and pancreatitis, decreased leptin level, hepatosplenomegaly, hepatic steatosis and hypertrophic cardiomyopathy. Clinical features, radiodiagnostic tests (Figure 2) and serum biochemistry were all compatible with the diagnosis of BSCL type 2. Muscular hypertrophy is present because of increased formation of muscle glycogen and creatinine. Some bone abnormalities could be detected by radiography and scintigraphy (8). The presence of acromegaloid characteristics such as prognatism in BSS is due to insulin-like growth factor (IGF) hypersecretion (3). Many BSCL patients have a normal glucose homeostasis early in life, with normal or slightly increased levels of insulin. Between 8 and 10 years of age, tolerance to glucose decreases quickly, and insulin resistance increases with age. Diabetes occurs, generally, at 12 years of age (8). In our case, the glucose tolerance test and HbA1c level was normal but HOMA-IR value for our case was 8.8 which was well above the cut-off point for diagnosis of insulin resistance in pediatric populations.

Although the etiology remained unknown, in a few reports several types of renal disorders with proteinuria and unique renal pathologies, including focal segmental glomerulosclerosis and membranoproliferative glomerulonephritis documented in individuals with BSCL (9). Although our case suffered from massive proteinuria, there was no evidence of specific renal disease in the patient's renal biopsy.

In all individuals with BSCL, the liver is affected, ranging from an abnormal liver functions to hepatic steatosis, hepatomegaly and cirrhosis. Ventricular dysfunction and hypertrophic cardiomyopathy are often observed in BSCL. In our case hypertrophic cardiomyopathy was detected. Hypertrophic cardiomyopathy in patient with BSCL has been correlated with high serum insulin levels, which activate the IGF1 receptors in the myocardial tissue (10).

The treatment of BSCL is not well established. Recent studies have proposed replacement with leptin, which has yielded promising results in controlling lipid and carbohydrate metabolic disorders, but the effects were limited (11). While an effective treatment is not available, controlling the diabetes, improving the insulin resistance, and reducing the triglyceride levels must be the aims. Diet is the most important aspect of management of BSCL individuals. The carbohydrate intake should be restricted and diet of patients with hypertriglyceridemia should contain low fat and high medium chain triglycerides (MCT) (12). Metformin has been shown to have some effect in helping patients reduce their appetite and improve hepatic steatosis (13).

In summary, with the exception of lytic bone lesions, this patient meets all the major and minor criteria for the diagnosis of Berardinelli-Seip congenital lipodystrophy type 2. This case who undiagnosed for many years applied with acute pancreatitis. Diagnosis could be managed by algorithmic approach to pancreatitis. Most of pediatricians approach to childhood pancreatitis by depending on adult physicians' experience and knowledge. However, as in this case, there are very different causes in children. While investigating the etiology of acute pancreatitis in children, this rare disease should be considered either.

Conflict of Interest: No conflict of interest was declared by the authors.

REFERENCES

1. Nydegger A, Couper RT, Oliver MR. Childhood pancreatitis. Gastroenterol Hepatol 2006; 21: 499-509.
2. Berardinelli W. An undiagnosed endocrinometabolic syndrome: report of 2 cases. J Clin Endocrinol Metab 1954; 14: 193-204.
3. Gomes KB, Pardini VC, Fernandes AP. Clinical and molecular aspects of Berardinelli-Seip Congenital Lipodystrophy (BSCL). Clinica Chimica Acta 2009; 402: 1-6.
4. Garg A. Acquired and inherited lipodystrophies. New Engl J Med 2004; 350: 1220–34.
5. Van Maldergem L, Magre J, Khallouf E, Gedde-Dahl T, Delepine M, Trygstad O, et al. Genotype phenotype relationships in Berardinelli Seip congenital lipodystrophy. J Med Genet 2002; 39: 722-33.
6. Bhayana S, Hegele RA. The molecular basis of genetic lipodystrophies. Clin Biochem 2002; 35: 171-7.
7. Magre J, Delepine M, Khallouf E, Gedde-Dahl T, Van Maldergem L, Sobel E, et al. Identification of the gene altered in Berardinelli-Seip congenital lipodystrophy on chromosome 11q13. Nat Genet 2001; 28: 365-70.
8. Oral EA, Simha V, Ruiz E, Andewelt A, Premkumar A, Snell P, et al. Leptin replacement therapy for lipodystrophy. New Eng J Med 2002; 346: 570-8.
9. Javor ED, Moran SA, Young JR, Cochran EK, DePaoli AM, Oral EA, et al. Proteinuric nephropathy in acquired and congenital generalized lipodystrophy: baseline characteristics and course during recombinant leptin therapy. J Clin Endocrinol Metab 2004; 89: 3199-207.
10. Bhayana S, Siu VM, Joubert GI, Clarson CL, Cao H, Hegele RA. Cardiomyopathy in congenital complete lipodystrophy. Clin Genet 2002; 61: 283-7.
11. Simha V, Szczepaniak LS, Wagner AL, Depaoli AM, Garg A. Effect of leptin replacement on intrahepatic and intramyocellular lipid content in patients with generalized lipodystrophy. Diabetes Care 2003; 26: 30-5.
12. Montenegro RM Jr, Montenegro AP, Fernandes MI, Moraes RR, Elias J Jr, Gouveia LM, et al. Triglyceride-induced diabetes mellitus in congenital generalized lipodystrophy. J Pediatr Endocrinol Metab 2002; 15: 441-7.
13. Pardini V, Victória I, Rocha S. Metformin improves metabolic control in subjects with Congenital Generalized Lipoatrophic Diabetes. In: 57th Annual Scientific Sessions, Boston-Massachusetts. Diabetes 1997; 46:160.