CASE REPORT

Report of Congenital Generalized Lipodystrophy in Children's Medical Center, Tehran, Iran

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ABSTRACT

Generalized lipodystrophy is a rare disorder in children characterized by absence of subcutaneous adipose tissue. We evaluated 10 patients with generalized lipodystrophy by skin and liver biopsy. Eight patients with steatohepatitis and cirrhosis were treated with Ursobile (uorsodeoxycholic acid) and vitamin E. In follow-up, serum triglyceride level was decreased.

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BACKGROUND

The lipodystrophy syndromes are rare diseases of childhood, characterized by the partial or generalized loss of adipose tissue. Partial lipodystrophy occurs more commonly in females than males and generally begins during the first decade of life.

Generalized lipodystrophy may be congenital or acquired.(1), Congenital generalized lipodystrophy was first described by Berardinelli in Brazil in 1954. It was then reviewed by Seip in 1959, and became known as Berardinelli-Seip syndrome.(2), It is a rare disorder with a prevalence of less than one per 12 million individuals.(3), The disease has an autosomal recessive inheritance and affects all ethnic groups. It is clinically characterized by loss of adipose tissue, especially subcutaneous fat, increased muscular growth, long extremities, cardiomyopathy and hepatosplenomegaly. Additional manifestations include advanced bone age, evidence of liver dysfunctions, dyslipidemia, glucose intolerance or diabetes mellitus, hyper insulinemia and cardiomegaly.(4)

The acquired types may be attributed to autoimmune disorders caused by infections.(5)

So far, two patients with lipodystrophy from Iran have been reported; one case form Mashhad (6) in year 2004, and another from Tehran.(7), Herein, we report on our experience with patients diagnosed with congenital lipodystrophy between April 2000 and July 2005 at the Children's Hospital Medical Center, Tehran, Iran.

MATERIALS AND METHODS

This is a retrospective study performed at the Children's Hospital Medical Center from April 2000 to July 2005.

Ten children aged between two months and five

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years (mean: 18.75 months) with propable lipodystrophy were enrolled into this study. For enrollment, a careful history and physical examination was done. Gender, age, and anthropometric data were recorded. Laboratory tests including a complete blood count (CBC), liver function test, lipid profile, blood sugar, blood urea nitrogen (BUN), creatinine level, insulin level, serum electrolytes, calcium, phosphorus, urinalysis, and stool examination were done for all patients. Chest and wrist x-rays and abdominal ultrasonography as well as skin and liver biopsy were done for all patients. Diagnosis of the disease was made based on clinical presentations and pathologic changes of liver (steatosis) and skin (absence of subcutaneous adipose tissue).

RESULTS

Ten patients (six males and four females) aged between two months and five years (mean: 18.57 months) were found to have congenital generalized lipodystrophy.

Growth retardation and low weight but tall height were found in all patients. Acanthosis nigricans was observed in one patient. Demographic data are presented in Table 1.

Sonography revealed liver hyperechogenicity (indicating fatty liver) in eight and coarse echogenicity (indicating cirrhosis) in two patients. One patient had the criteria of rickets on his wrist roentgenogram.

Laboratory test results, before and after treating the patients, are presented in Table 2. The mean triglyceride (TG) and alanine aminotrasferase (ALT) was decreased significantly ($P<0.05$) after treatment.

Pathologic findings of liver biopsy are presented in Table 3.

No cardiomyopathy and diabetes mellitus was found in patients.

Triangular facies, tall stature and increased muscle mass are evident in Figures 1 and 2.

All patients were treated with Ursobile

Table 1. Demographic data.

Signs / patient	I	II	III	IV	V	VI	VII	VIII	IX	X
Generalized lipoatrophy	+	+	+	+	+	+	+	+	+	+
Muscular hypertrophy	+	+	+	+	+	+	+	+	+	+
Triangle facies	+	+	+	+	+	+	+	+	+	+
Hepatosplenomegaly	+	+	+	+	+	+	-	+	+	+
Growth retardation and low weight gain	+	-	-	+	+	+	+	+	+	+
Hypertrichosis	-	-	-	-	-	-	-	-	-	+

Table 2. Laboratory test results

Parameter (Serum)	Before treatment		After treatment		p-value
	Mean	SD	Mean	SD	
Cholesterol	207.8	111.66	157.9	102.96	0.07
Triglycerides	706.2	711.71	425.5	333.72	0.05
AST	108.1	111.05	52.6	32.93	0.06
ALT	85.7	84.64	45.9	30.31	0.05

Table 3. Results of liver biopsy.

Patient / finding	Age of patients	Liver biopsy
I	3 M	Normal
II	5 M	Microsteatosis
III	2 M	Steatohepatitis
IV	11 Y	Liver cirrhosis
V	5 Y	Steatohepatitis
VI	11 Y	Steatohepatitis with areas of nodular fibrosis
VII	3 Y	Steatohepatitis
VIII	2.5 Y	Steatohepatitis
IX	3 Y	Steatohepatitis
X	2 M	Steatohepatitis

Figure 1. Case III, a 6 month-old boy.

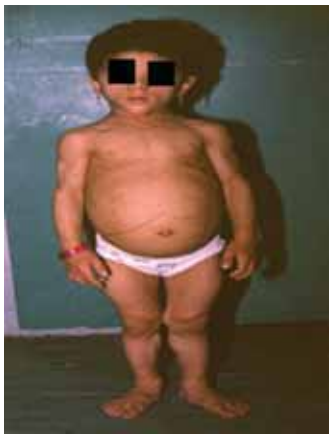

Figure 2. Case VI, a 2.5-year-old girl.

(ursodeoxycholic acid), vitamins (including vitamin E) and trace elements.

Infants under six months of age were on breast feeding and formula (milk cuprilon: 75% fat of MCT⋆ oil). After six months of age, besides to breast feeding, patients were fed with complementary foods and MCT oil.

During the mean follow-up of 63 months, all patients were doing well and their serum TG and ALT levels were decreased.

DISCUSSION

Congenital generalized lipodystrophy is a rare autosomal recessive disease, with a quite characteristic phenotype. Lack of subcutaneous adipose tissue and muscular hypertrophy are

⋆ Medium Chain Triglycerides

prominent from the first month of life, and low weight gain is frequently observed.(2, 8), The definite diagnosis of the disease in our patients was made on characteristic pathologic findings of skin biopsy, i.e., loss of subcutaneous fat. In our study, two patients were siblings.

Enlarged extremities (hands, feet, ears and nose) were observed in all patients, giving them an acromegalic appearance.

Other common findings include curly and frizzy hair, dry and thick skin, hypertrichosis, hyperhidrosis, and large prominent superficial veins.(4, 5, 8, 9), In this study, one patient had hypertrichosis.

The morphological and functional study of the skeletal musculature of patients with this disease suggests that the increased muscle mass results from hyperplasia rather than hypertrophy, showing no association with increased strength.(10)

Accumulation of TG and glycogen in hepatocytes, may cause hepatosplenomegaly which accompanied abnormal liver function test that may lead to cirrhosis.(2-5, 8, 9)

Hpertriglyceridemia may result in small fat deposits known as xanthomas, which occurs in the palmar, joint, perioral regions and foot.(4, 9, 11), None of our patients had xanthomas. Impaired carbohydrate metabolism is characterized by primary peripheral insulin resistance associated with hyperinsulinemia which, after puberty, results in secondary diabetes mellitus. This finding is related to insulin post-receptor defects in adipocytes, hepatocytes and muscle cells which also participate in the etiology of hyperlipidemia. These patients are resistant to insulin or oral hypoglycemic agents. Among the reported patients, two females had diabetes and one had hyperinsulinemia. (9-11), In our study, hyperinsulinemia was found in two patients, though their blood sugar was normal. The anabolic process is easily perceived through a rapid increase in height, increased muscle mass, skeletal sclerosis and enlarged organs. A hypermetabolic state secondary to this process has probably a protective effect, explaining the more severe metabolic disorder that occurs after puberty.(12, 13)

These findings were observed in all of our patients. Enlarged organ (especially, hepatosplenomegaly) were seen in nine patients. The x-ray of the long bones revealed sclerotic areas in one patient.

Despite of delayed menarche that attributed to liver cirrhosis, pubarche in affected girls occurs early. None of our patients had cardiomyopathy nor nephropathy. One patient had liver cirrhosis.

Patients were managed by a multidisciplinary team (pediatrics gastroenterologists, endocrinologists and nutritionists).

All patients were placed on restricted saturated fats; simple carbohydrates were replaced by complex carbohydrates, soluble fibers, medium-chain TG and unsaturated fatty acids. The proper control of triglyceridemia may delay the development of diabetes mellitus. Our patients with hypertriglyceridemia and increased serum aminotransferase levels (ALT, AST) were received Delursan (urosodeoxycholic acid) and vitamin E. Recent studies have proposed replacement therapy with leptin, a protein produced by adipose tissue that plays an important role in homeostasis of energy, which has yielded promising results in controlling lipid and carbohydrate metabolic disorders that are characteristics of this syndrome.(14)

CONCLUSION

The phenotypic characteristics of congenital generalized lipodystrophy are well identified, which in most of cases, favors the clinical diagnosis. The congenital generalized lipodystrophy is a wery unusual syndrome that illustrates the importance of the adipose tissue for the majority of metabolic processes. A better understanding of this syndrome may open new horizons in the research of more prevalent disease such as diabetes mellitus and obesity.

★ Aspartate Aminotransferase

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