Congenital Generalized Lipodystrophy in a 4-Month-Old Infant

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Abstract: Congenital generalized lipodystrophy (CGL, Berardinelli-Seip syndrome) is a rare autosomal recessive disorder with a clinical presentation of paucity of adipose tissue, muscular hypertrophy, organomegaly, and insulin-resistant diabetes. A 4-month-old Taiwanese female infant had hepatosplenomegaly and low body weight gain despite a voracious appetite. Hypermetabolism, hyperhidrosis, loss of subcutaneous fat, muscular hypertrophy, acanthosis nigricans, hypertrichosis, and marked hypertriglyceridemia were also noted. Liver histology revealed fatty change and portal-to-portal bridging fibrosis. Clinical features, serum biochemistry, and liver histology were compatible with the diagnosis of CGL. She was given a special diet characterized by calorie restriction and partial substitution of long-chain triglycerides with medium-chain triglycerides. The serum triglyceride concentration subsequently decreased. This present case suggests that extensive fatty infiltration and subsequent cirrhosis of the liver may be the earliest complication of CGL.

Generalized lipodystrophy can be classified into two types, congenital generalized lipodystrophy (CGL) and acquired generalized lipodystrophy (AGL) [1]. CGL (also known as Berardinelli-Seip syndrome), first described by Berardinelli in 1954 [2], is inherited in an autosomal recessive pattern and is usually characterized in infancy. Its etiology is still unknown; however, an inability to store energy in adipose tissue is of pathogenetic importance. In CGL, insulin resistance is present from birth, resulting in hyperinsulinemia, hyperlipidemia, and insulin-resistant diabetes with an anabolic syndrome worsened by a voracious appetite [1]. Insulin resistance is characterized by a heightened concentration of circulating insulin in the presence of normal or elevated blood glucose concentrations [3]. Studies have suggested that the metabolic abnormalities of CGL may be related to the insulin receptor, pre-receptor, or post-receptor [1, 3–6]. The diagnosis of CGL is made mainly via characteristic clinical features, including extreme paucity of adipose tissue, muscular hypertrophy, increased height velocity in pre-school age children, organomegaly with hypertrophic cardiomyopathy, and insulin-resistant diabetes [1]. Light and electron microscopy findings from liver biopsy specimens may help confirm the diagnosis. Histopathologic changes include steatosis and periportal fibrosis, with portal-to-portal bridging; the presence of fat and glycogen is demonstrated by special stain in the cytoplasm of hepatocytes [7]. Significant ultrastructural findings include high fat deposition in the cytoplasm, modifications to the mitochondria, and a growing number of peroxisomes. These ultrastructural changes may be related to disordered lipid metabolism [7–10].

AGL (also known as Seip-Lawrence syndrome) is sporadic and its clinical picture is similar to that of CGL. The anabolic syndrome of AGL, however, is more variable and milder, depending on the age of onset and the triggering events. AGL may be caused by the destruction of adipose tissue by an autoimmune mechanism [1].

We report a case of CGL with an extremely early onset and liver cirrhosis. The clinical features, liver

histology, and electron microscopy findings in this patient are also discussed.

Case Report

This 4-month-old female infant was born to a G1P1 healthy mother via vaginal delivery at a gestational age of 39 weeks and a birth weight of 3,055 g. Her parents were non-consanguineous Taiwanese. There was no family history of congenital disease. The mother noted that the infant suffered poor body weight gain and abdominal distension from the neonatal period, although the baby's appetite was good. At 2 months old, her head circumference was 39.5 cm (75–95th percentile), body length 56 cm (25th percentile), body weight 3.9 kg (< 3rd percentile), and body mass index (BMI) 12.4 kg/m^2 (< 5th percentile). Marked hepatomegaly (7 cm below the right costal margin) was also noted. Fasting blood glucose was 9.6 mmol/L, triglyceride 17.8 g/L, cholesterol 3.6 g/L, and alkaline phosphatase (ALP) 1,441 U/L. Serum aminotransferase, γ-glutamyl transferase (γ-GT), blood urea nitrogen (BUN), creatinine (Cr), albumin, globulin, uric acid, and lactic acid concentrations as well as complete blood count were within normal limits. Abdominal sonography revealed homogeneous hepatomegaly. Liver histology revealed fatty metamorphosis. At 4 months old, her body weight was 7 kg (75th percentile), BMI 17.6 kg/m^2 (near the 90th percentile), body length 63 cm (50–75th percentile), and head circumference 43.5 cm (97th percentile). Physical examination showed a generalized lack of subcutaneous fat, prominent muscular hypertrophy (triceps skin fold < 5th percentile, circumference of middle of upper arm muscle 50th percentile), acanthosis nigricans, abundant curly scalp hair, and hypertrichosis of both arms (Fig. 1). The liver was 15 cm below the right costal margin and the spleen was 3 cm below the left costal margin. The external genitalia were normal. A voracious appetite with hyperhidrosis was noted. Neurologic development was slightly delayed. The following fasting serum concentrations were noted: triglyceride 8.6 g/L, cholesterol 3.3 mmol/L, low-density lipoprotein 0.13 mmol/L, high-density lipoprotein 0.52 mmol/L, glucose 6.5 mmol/L, insulin 158.9 μU/mL, glycosylated hemoglobin (HbA1c) 4.7%, aspartate aminotransferase (AST) 59 U/L, and alanine aminotransferase (ALT) 40 U/L. Normal blood concentrations were noted for BUN, Cr, bilirubin, albumin, globulin, ammonia, lactic acid, γ-GT, electrolytes, 17-hydroxyprogesterone, androsterodione, testosterone, follicle-stimulating hormone, and luteinizing hormone, and the complete blood count was also normal.

Brain sonography and magnetic resonance imaging (MRI) revealed prominent sulci, wide subarachnoid space, mild subdural fluid collection at the left interhemispheric region and overlying the right frontoparietal area, and decreased white matter at the occipital lobe (Fig. 2). Electromyography was normal. Cardiac sonography showed a mild hypertrophic interventricular septum (interventricular septum: 0.95 cm, left ventriclar posterior wall: 0.65 cm). Abdominal sonography revealed a huge liver with homogenously increased echogenicity, and bilateral nephromegaly. Liver his-

Fig. 1. *Four-month-old girl with a generalized deficiency of subcutaneous fat, muscular body build, hepatosplenomegaly, acanthosis nigricans, and hypertrichosis in both upper arms.*

tology at 4 months of age showed a marked fatty change in hepatocytes, portal-to-portal bridging fibrosis, and separation of lobules into tiny nodules by fibrous tissue (Fig. 3). Ultrastructurally, the hepatocytes were filled with fat and glycogen, and the mitochondria were misshapen with the rarefaction of cristae and prominent mitochondrial matrix granules. The numbers of peroxisomes and lysosomes were increased (Fig. 4).

CGL was diagnosed based on clinical findings, biochemical features and liver histology. To control the hyperlipidemia and high anabolic status of the patient, we designed a modified formula based on the reduction of dietary fat intake, partial substitution of medium-chain triglycerides (MCT) for dietary long-chain triglycerides (LCT), and caloric restriction (fat content reduced to 35% of total calories, MCT/LCT ratio 0.5, essential fatty acids 4% total calories, maximal caloric restriction 740 kcal/day). During the 6-month follow-up period, her body weight was kept within the 75th to 90th percentile, fasting blood glucose was within normal limits, serum triglycerides were markedly decreased and stayed around 2.4 g/L, but serum aminotransferase was still mildly elevated (AST 74U/L, ALT 91U/L). The initial results of our therapy were acceptable, as shown by serum triglyceride concentrations.
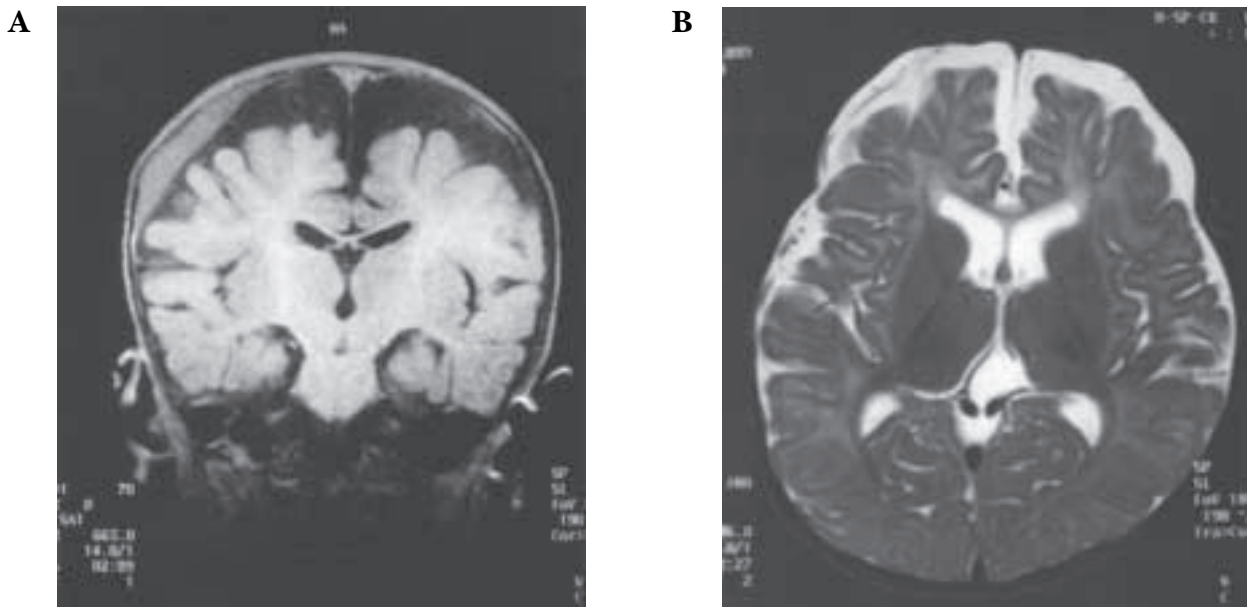
Fig. 2. *Brain magnetic resonance imaging (MRI) scan: A) coronal T1-weighted MRI scan shows prominent sulci, wide subarachnoid space, and mild subdural fluid collection. B) Cross-section T2-weighted MRI scan shows decreased white matter at the occipital lobe. Milestones of myelination are within normal limits.*

Discussion

Our patient had an increased number of lysosomes in hepatocytes. The reason for this increase remains elusive. The progression of liver fibrosis between the first and second liver biopsy over a 2-month interval was very rapid. The liver in patients with CGL is affected to varying degrees, ranging from an abnormal liver function test to cirrhosis [11–15]. None of the previously reported cases developed liver cirrhosis as early as our patient. In one previously reported case, steatosis of the liver was observed as early as 19 months of age in a patient with CGL, who later developed severe cirrhosis and died of hepatic failure [12]. Autopsy of patients with CGL showed marked hepatomegaly, severe fatty infiltration, and fibrosis in an 18-month-old boy [13], and cirrhosis in a 12-year-old girl [14]. However, autopsy of a 24-year-old girl with CGL showed only hepatomegaly with fatty infiltration of the liver [15]. Cirrhosis and its complications may cause significant morbidity and mortality in CGL, and close follow-up of the liver status is necessary.
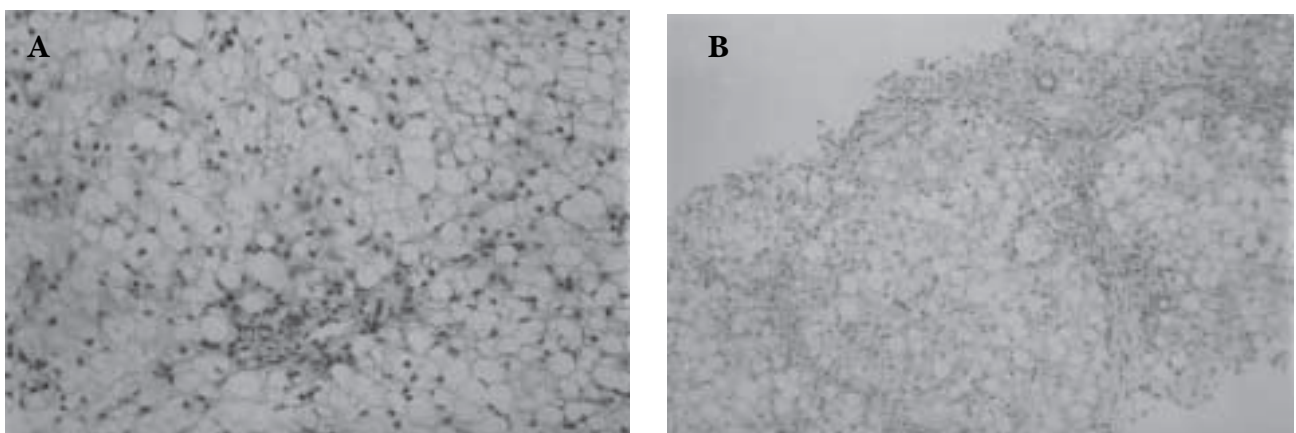

Fig. 3. *Liver histology taken at A) 2 months shows fatty change of hepatocytes (hematoxylin and eosin, x 200) and B) at 4 months shows glycogen deposition and severe fatty change of hepatocytes with portal-to-portal fibrosis (hematoxylin and eosin, x 100).*
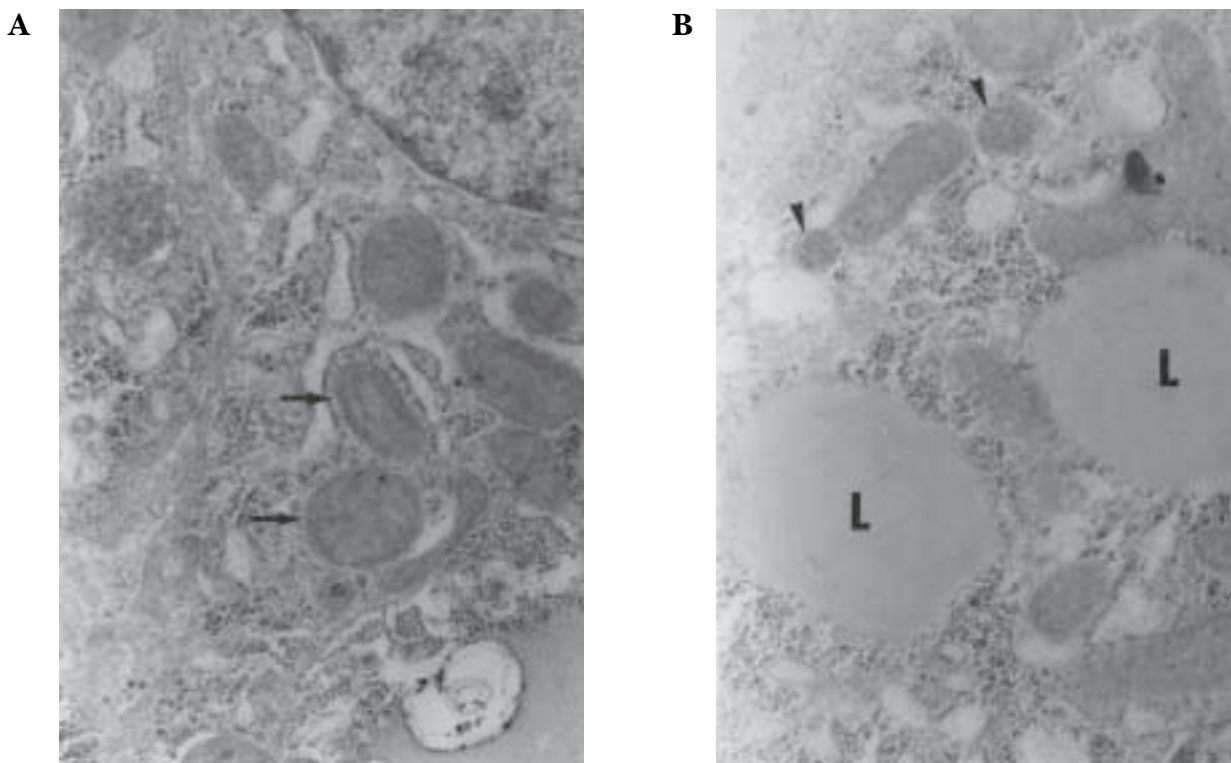
A

B

Fig. 4. *Electron micrograph reveals A) misshapen mitochondria with rarefaction of cristae and prominent matrix granules and B) increased numbers of peroxisomes (arrowhead) and lipid droplets (L). (x 12,000)*

CGL also involves the brain. Most CGL patients have below average intelligence; some have dilated brain ventricles and basal cisterns as well as brain atrophy [1, 16]. Decreased brain white matter in CGL has not been previously reported, but this finding suggests the need for brain imaging.

The CGL gene is found in chromosome 9q34, which harbors a plausible candidate gene encoding the retinoid X-receptor-α (RXRA). RXRA plays a central role in adipocyte differentiation [17]. Recently, a new mutation in a gene encoding a nuclear protein, lipin (which is responsible for lipodystrophy), has been identified in a mouse model [18].

Due to the similar clinical appearance between leprechaunism and CGL, these two diseases should be differentiated. Leprechaunism is characterized by intrauterine growth retardation and poor growth during the postnatal period, fasting hypoglycemia, and postprandial hyperglycemia in association with insulin resistance.

Although there is no effective therapy available for CGL, caloric restriction is very important. This can reduce anabolic processes and delay diabetic com-plications, progression of hypertrophic cardiomyo-pathy, and liver cirrhosis. Fenfluramine, an appetite suppressant, may be effective as an adjunctive therapy to reduce calorie intake [1, 19, 20]. Eucaloric substitution of MCTs for dietary long-chain fatty acids resulted in the improvement of hypertriglyceridemia, carbohydrate intolerance, and reduced hepatomegaly in an AGL patient [20]. In our patient, the serum triglyceride concentration was markedly decreased, liver size was still enlarged, while serum aminotransferase was mildly elevated. Studies using a lypodystrophic mouse model have shown that insulin resistance could be overcome by continuous systemic infusion of low doses of recombinant leptin [21]. Further study is needed to determine the safety and efficacy of this modality in humans.

In summary, CGL is a multi-systemic and progressive disease. Early onset of liver cirrhosis in infancy may occur and cause significant morbidity and mortality. In addition, diabetic renal failure [1, 11] and hypertrophic cardiomyopathy [22, 23] are potentially lethal complications. Early diagnosis and diet control can bring about a favorable outcome.

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