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CONGENITAL GENERALIZED LIPODYSTROPHY: BERARDINELLI SYNDROME*

Report of Two Siblings

*Figen Gürakan MD***, *Nurten Koçak MD****, *Aysel Yüce MD*****

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Two successively born infants with Berardinelli syndrome, an unusual lipodystrophic disease, are reported. In addition to hepatomegaly, accelerated growth, muscle hypertrophy, lack of adipose tissue, hirsutism and hypertriglyceridemia, which are the characteristics of the syndrome, these brothers demonstrated bilateral, symmetrical, renal medullary hyperechogenicity, which has not before been reported in association with generalized lipodystrophy. Although more than 25 cases have been recorded, the metabolic defect responsible for this inborn error of metabolism has not yet been determined. *Key words: Berardinelli syndrome, lipodystrophy.*

Congenital generalized lipodystrophy (CGL), also known as Berardinelli syndrome, is a rare genetic disorder transmitted as an autosomal recessive trait and characterized by extreme paucity of fat in adipose tissue from birth. Berardinelli first reported this unusual syndrome in 1954 in two children with acromegaloid gigantism, hepatosplenomegaly, fatty infiltration of the liver, hyperlipidemia, hyperproteinemia and disturbed carbohydrate metabolism[1]. Coarse and hyperpigmented skin, hirsutism with curly scalp hair, large superficial veins, phallic enlargement, hypertrophy of muscle with excess glycogen, acanthosis nigricans, cardiomegaly, corneal opacities and variable mental deficiency are the other features of the disease. While accelerated growth and hypertriglyceridemia are most prominent in early childhood, diabetes mellitus, insulin-resistant non-ketotic hyperglycemia, hyperinsulinism and cirrhosis may develop in later childhood or adulthood[2]. Here we report two brothers who are believed to have CGL with specific clinical findings.

Case Reports

Case 1

A seven-month-old boy was admitted to the hospital with a prominent abdomen and failure to gain weight. The child was the first product of a third-degree

* From the Gastroenterology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Pediatrician and Fellow in Pediatric Gastroenterology, Hacettepe University Faculty of Medicine.

*** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

consanguineous marriage. The baby was born after an uncomplicated pregnancy, weighing 2700 g. On admission, physical examination revealed a weight of 5600 g (5^{th} percentile), height of 68 cm (50^{th}-75^{th} percentile) and head circumference of 42 cm (10^{th} percentile). The patient displayed marked abdominal protrusion with a palpable liver having soft, regular borders approximately 7 cm below the right costal margin and 8 cm below the xiphoid. The spleen was palpable 1 cm below the left costal margin. He had a peculiar, cachectic face with the appearance of an old man. Psychomotor development was normal. Special mention should be made of the advanced muscular development of the limbs and lack of subcutaneous fat. The muscles were bulky, firm and well-shaped with thick, large superficial veins. The skin was also thick and dry with little fat or turgor. The child had large hands, feet and joints. Although his back and limbs were covered with fine hair, the pubis and axillae were free of hypertrichosis. He had well-developed genitalia.

Routine laboratory tests were normal, including blood cell counts, electrolytes, glucose, creatinine, urea nitrogen, aspartate amino transferase, alanine amino transferase, alkaline phosphatase, uric acid, albumin, cholesterol, pH and blood gases. Prothrombin and partial thromboplastin times were also normal. Serum total protein, calcium and phosphorus levels were high (11.6 g/dl, 11.7 mg/dl and 6.2 mg/dl, respectively). The triglyceride level was much higher than normal (1715 mg/dl). Lipid electrophoresis revealed an increase in the pre-beta region that corresponded to type IV hyperlipidemia. His parents' biochemical tests were normal. Urinalysis, daily urine oxalate excretion, ratio of calcium to creatinine in spot urine, serum parathormone, and complement 3 and 4 levels were within normal limits. Plasma and urinary aminoacid chromatography revealed relatively high glycine, serine, glutamine and basic amino acids. Abdominal ultrasonography revealed hepatosplenomegaly with diffuse steatosis of the liver, bilateral renomegaly with increased parenchymal echogenicity and medullary enlargement together with hyperechogenic, symmetrical lesions. Histopathologic examination of the liver obtained by needle aspiration biopsy indicated diffuse, large, vacuolated steatosis. Mild radiographic cardiomegaly was evident, but the electrocardiogram and echo-cardiogram were normal as well as the cardiac sounds. His bone age was five months older than his chronological age. Neither hyperinsulinism nor hyperglycemia was noted during follow-up. At 16 months of age, his weight was 10.6 kg and his height was 83 cm (25^{th}-50^{th}, and 75^{th} percentiles, respectively). The parents complained of frequent respiratory tract infections. Serum total protein and calcium levels were normalized and the triglyceride level lowered (656 mg/dl) without any medication.

Case 2

A three-month-old infant, the brother of the first patient, displayed the same clinical findings of the disease. His weight was 5 kg and height 61 cm (10^{th}-25^{th} and

50th percentiles, respectively). Subcutaneous fat was absent on his face and in the gluteal region, his liver was palpable 4 cm below the costal margin, and his muscles were hypertrophic. Hypertriglyceridemia (620 mg/dl), advanced bone age (6-9 months), ultrasonographic findings of hepatomegaly and renal medullary hyperechogenicity revealed the syndrome. Blood cell counts, glucose, creatinine, urea nitrogen, aspartate and alanine aminotransferases, alkaline phospatase, uric acid, total protein, albumin, cholesterol, calcium and phosphorus levels of serum, as well as urinalysis and the ratio of calcium to creatinine in spot urine were in the normal ranges.

Discussion

The patients' findings suggested Berardinelli syndrome (Figs. 1-4). This very rare syndrome was first reported from Brasil[1]. Later several cases were reported from the United States, Norway, Great Britain, Germany and France[3,4]. Autosomal recessive inheritance is suggested for this syndrome.

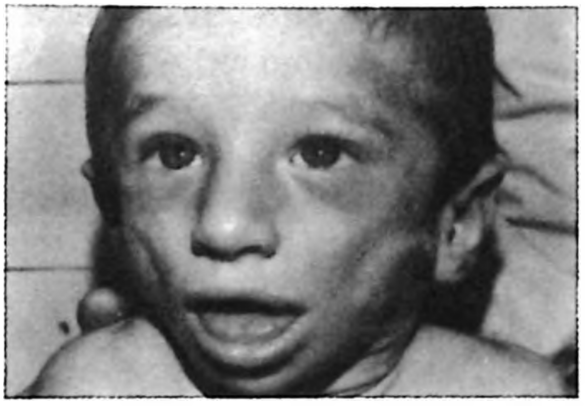

Fig. 1: Cachectic face of Case 1 (nine months old).

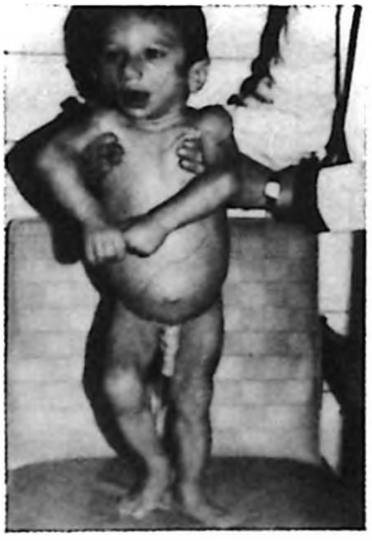

Fig. 2: Muscle hypertrophy, hepatomegaly and hirsutism of Case 1 (nine months old).

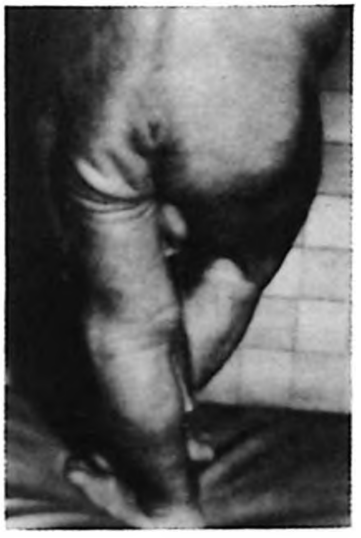

Fig. 3: Lack of adipose tissue in gluteal region of Case 1 (nine months old).

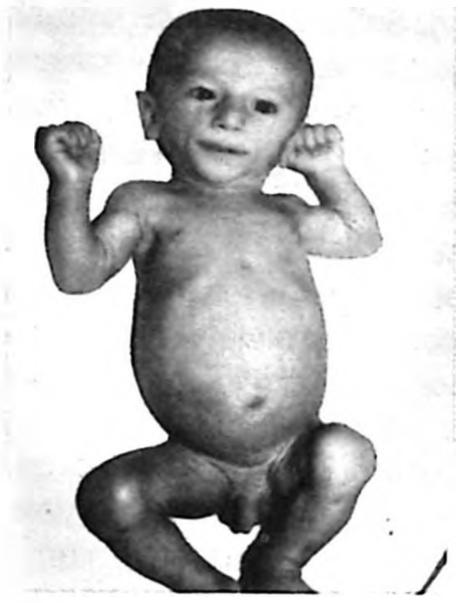

Fig. 4: Note the cachectic face and muscle hypertrophy of Case 2, three months old.

In total generalized lipodystrophy, there is said to be a complete loss of adipose tissue, either evident at birth or appearing later in life, together with a number of associated features, commonly including hepatomegaly, hyperglycemia and hyperlipidemia. The liver is affected in all patients. Histology reveals combinations of periportal foci of round cell infiltration, nuclear syncytial formation, fatty infiltration, glycogen deposition and fibrosis. Fibrosis seems progressive, and some patients have died of hepatic failure or bleeding esophageal varices[3]. One of our patients underwent liver biopsy, which revealed steatosis but no fibrosis.

Hyperglycemia is commonly considered a major and constant component of CGL. All adults have been affected, but this has not been evident in several of the younger patients[4]. In fact, our patients' glucose levels were normal. Generalized lipoatrophy may also occur as an acquired condition, often combined with diabetes (lipoatrophic diabetes)[5].

Partial lipodystrophy is more frequent, particularly affects females, and is characterized by loss of facial fat alone or with involvement of the neck, arms, chest and abdomen; however, fat deposition over the legs is normal or even increased. In addition to the strikingly cadaverous appearance, these patients usually have renal and liver involvement with complement abnormalities[6]. In contrast, patients with Berardinelli syndrome have displayed normal complement levels[7], as did our older patient.

Hyperlipidemia, which is most notable during the first years of life, has been present in most reported patients, and the increase confined almost solely to the triglyceride moiety. In accordance with this, our patients revealed high triglyceride levels. Although the triglyceride levels of some patients' parents have

been found to be higher than normal, we could not demonstrate this. A substantial portion of such patients exhibit disorders of the kidneys (nephrotic syndrome or nephromegaly). Our patients had nephromegaly and medullary hyperechogenity, findings which have not been reported before. Central nervous system anomalies, including ventricular dilatation and mental retardation, have been reported[8]; however, the neurological findings of our cases were normal. Cardiomegaly, another component of the syndrome, has been found to be more pronounced with increasing age. Among adult patients, mild hypertension and nonobstructive hypertrophic cardiomyopathy have also been reported[9].

Gang et al.[10] recently showed with whole-body magnetic resonance imaging (MRI) in three patients with CGL that fat was present in areas where it might be serving mainly a mechanical function, such as in the orbits, palms, soles, periauricular and epidural regions; and to a lesser extent in the tongue, breasts, vulva and buccal area, but not in other subcutaneous areas, in the intraabdominal and intrathoracic regions or the bone marrow. These researchers believe that the genetic defect in CGL results in poor growth and development of metabolically active adipose tissue.

Although accelerated growth and maturation plus muscular hypertrophy and enlargement of the phallus are suggestive of an androgen effect, neither and rogens nor gonadotropins are elevated[11], and hirsutism does not include pubic and axillary hair, as in our elder patient.

The pathogenesis is quite obscure, and no ready hypothesis suggests itself to explain satisfactorily so many diverse features. A primary disorder of the fat-storing cells might lead to hyperlipidemia, hyperglycemia and a fatty liver as a consequence of loss of the major storage organ for calories. However, accelerated growth, bone maturation, pigmentation, hirsutism, genital enlargement and increase of muscle mass are not easily explicable. One postulate is that absence of an important target organ, adipose tissue, might result in oversecretion of hormones. There is another postulate of a hypothalamic disorder causing release of a fat-mobilizing agent. This regulation of normal adipose tissue function might also result in lipoatrophy. Another explanation is the increased activity of the adrenergic nervous system resulting in lipoatrophy because of the lipolytic effects of the catecholamines. Guanfacine, a supressor of adrenergic activity, however, did not yield any increase in the adipose tissue of a partial lipodystrophy patient[12].

A factor contributing to the variability of the features of the syndrome is the age at which the patient is observed. As hyperglycemia and cardiac changes are the features of older ages, our patients will be carefully observed for those symptoms throughout their lives.

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