Congenital Generalized Lipodystrophy

Congenital generalized lipodystrophy (CGL), also called Berardinelli-Seip syndrome (BSCL), is an extremely rare genetic disorder characterized by extreme paucity of adipose tissue from birth, extreme insulin resistance, hypertriglyceridemia, hepatic steatosis, and early onset of diabetes. Its prevalence is estimated to be less than 1 in 12 million people.

GENETICS/BASIC DEFECTS

1. Inheritance: autosomal recessive
2. Existence of two loci in a gene for congenital generalized lipodystrophy (Berardinelli-Seip congenital lipodystrophy)
   a. Congenital generalized lipodystrophy type 1
      i. Identification of the aberrant gene, 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) in patients from several pedigrees in which the lipodystrophy was linked to chromosome 9q34
      ii. Several homozygous or compound heterozygous mutations in the *AGPAT2* gene identified in affected patients
      iii. *AGPAT2* (1-acylglycerol-3-phosphate O-acyltransferase 2)
         a) Encodes the enzyme AGPAT2 that is responsible for the production of an important intermediate in the synthesis of triglycerides or fat
         b) Mutations of *AGPAT2*: may cause CGL by inhibiting the fat synthesis and storage in adipocytes (fat cells)
   b. Congenital generalized lipodystrophy type 2
      i. Identification of another disease locus (*BSCL2*) which is mapped to chromosome 11q13
      ii. Identification of mutations of *BSCL2* gene in all families linked to 11q13
      iii. *BSCL2* (*Seipin*) gene
         a) Highly expressive in the brain and testis
         b) Encodes a protein whose function remains unknown
3. Several other genes are responsible for different types of inherited lipodystrophies:
   a. Lamin A/C (*LMNA*) gene in familial partial lipodystrophy Dunnigan variety (autosomal dominant familial partial lipodystrophy) mapped to 1q21–22
   b. *PPAR-γ* (peroxisome proliferator-activated receptor-γ) gene in autosomal dominant familial partial lipodystrophy
4. Cause
   a. CGL is caused by mutations in *BSCL2, AGPAT2,* and other as yet unmapped genes
   b. This genetic heterogeneity is also accompanied by phenotypic heterogeneity
5. Proposed pathogenesis: genetic defect results in poor growth and development of metabolically active adipose tissue with preservation of mechanical disposition of the adipose tissue

CLINICAL FEATURES

1. Extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized muscular appearance (an essential diagnostic criterion)
2. Characteristic features during early childhood
   a. Accerated linear growth
   b. Voracious appetite
   c. Increased basal metabolic rate (hypermetabolism)
   d. Advanced bone age
3. Acanthosis nigricans (dark velvety pigmentation of the skin)
   a. Common occurrence
   b. Usually appears by age 8
   c. May be widespread, involving the neck, axillae, groin, and trunk
   d. Can eventually cause skin tag formation
4. Umbilical hernia: common
5. Hepatosplenomegaly
   a. Almost universal presence of hepatomegaly from fatty liver, ultimately leading to cirrhosis
   b. Splenomegaly common
6. Acromegaloid appearance
   a. Enlarged hands and feet
   b. Prominent mandible
7. Premature thelarche and adrenarche
8. Affected women
   a. Virilization (clitoromegaly and hirsutism)
   b. Oligo-amenorrhea
   c. Polycystic ovaries in postpubertal female patients
   d. Successful pregnancy rare
9. Affected males with normal reproductive potential
10. Multiple focal lytic lesions in the appendicular bones in postpubertal patients
11. Severe fasting and postprandial hyperinsulinemia and marked hypertriglyceridemia resulting in chylomicronemia, eruptive xanthomas, acute pancreatitis and predisposing to premature atherosclerosis
12. Abnormal glucose intolerance and diabetes mellitus develop during puberty or early adolescence. Diabetic nephropathy and nephropathy may develop during adulthood
13. Rare hypertrophic cardiomyopathy
14. Mental retardation in a few patients

DIAGNOSTIC INVESTIGATIONS

1. Clinical laboratory work-up
   a. Marked insulin resistance
   b. Severe hyperinsulinemia
   c. Nonketotic insulin-resistant diabetes mellitus
   d. Hypertriglyceridemia with low serum high-density lipoprotein (HDL) and cholesterol concentration
   e. Chylomicronemia
   f. Markedly low plasma leptin levels

2. MRI (confirmatory) and necropsy
   a. An extreme paucity of subcutaneous and intermuscular fat
      i. Intraabdominal sites (omental, mesenteric, and retroperitoneal areas)
      ii. Thoracic cavity (retrosternal, epicardial, and superior mediastinal areas)
      iii. Bone marrow
      iv. Parathyroid glands
   b. In contrast, a peculiar distribution of normal amounts of adipose tissue over whole body
      i. Orbits
      ii. Crista galli
      iii. Palms
      iv. Soles
      v. Scalp
      vi. Perineum
      vii. Vulva
      viii. Epidural area
      ix. Pericalyceal regions of the kidney
      x. Periarticular regions (knee, hip, shoulder, elbow, wrist, and ankle joints)
      xi. Some fat localizes in breasts, tongue, and buccal region
3. Skeletal radiography: multiple focal lytic lesions appear in appendicular skeletons after puberty
4. Echocardiography to detect hypertrophic cardiomyopathy
5. Molecular genetic analysis of mutations in *BSCL2* (Seipin) gene and *AGPAT2* gene

GENETIC COUNSELING

1. Recurrence risk
   a. Patient's sib: 25%
   b. Patient's offspring: not increased unless the spouse is a carrier or affected
2. Prenatal diagnosis: not reported
3. Management (Garg, 2004)
   a. Cosmetic management
      i. Facial reconstruction with free flaps, transposition of facial muscle, and silicone or other implants in the cheeks
      ii. Liposuction or lipectomy for removal of excessive facial or neck fat
      iii. Etretinate and fish oil may improve acanthosis in some patients
   b. Diet
      i. Avoidance of weight gain to reduce the risk of developing diabetes and dyslipidemia
      ii. Need sufficient energy to allow for growth and maturation in childhood
   c. Hypoglycemic drugs
      i. Require rigorous glycemic control
      ii. Require large dose of insulin to control hyperglycemia and prevent long-term complications of diabetes, such as nephropathy, retinopathy, neuropathy, and possibly atherosclerosis
   d. Lipid-lowering drugs
      i. Fibrates and, if needed, n-3 polyunstaurated fatty acids
      ii. Avoid estrogens for oral contraception or postmenopausal hormone replacement therapy in women because it can accentuate hypertriglyceridemia
   e. Clinical trial of adipocytes hormone leptin-replacement therapy has shown a marked reduction in the blood glucose and lipids and reverse hepatic steatosis, allowing discontinuation of several medications

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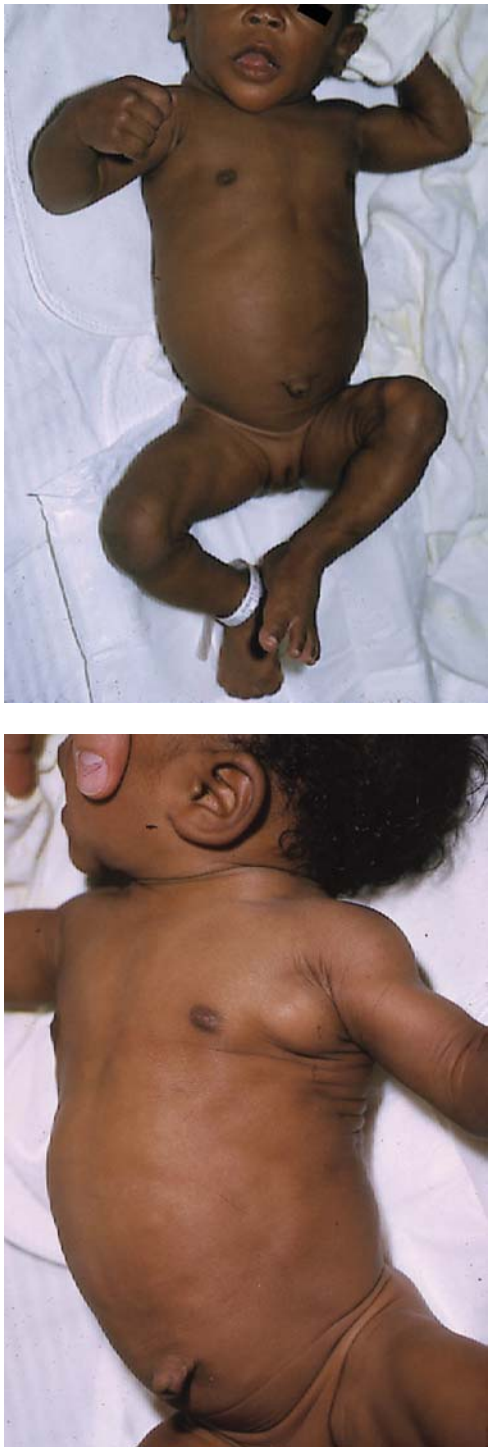

Fig. 1. An infant with congenital generalized lipodystrophy showing extreme paucity (near complete absence) of adipose tissue from birth, resulting in a generalized prominent muscular appearance