Congenital Generalised (CGL; Berardinelli-Seip Syndrome)

This is a rare autosomal recessive disorder of the adipose tissue. In an autosomal recessive disorder, parents are carriers of the genes but are not affected. The risk increases with consanguinity (when parents are close relatives e.g. uncle-niece, cousins etc). There is a 25% chance of transmission of both defective genes to the affected children. That is the ratio of affected to unaffected children is 1:3.The lipodystrophy is characterised by near complete absence of body fat. This condition is sometimes refered to as "Total body lipodystrophy".

There are two types of congenital generalised lipodystrophy, CGL1 due to AGPAT2 gene mutations (alterations or abnormalities) and CGL2 due to BSCL2 gene alterations. Compared to CGL1, CGL2 patients have more severe lack of body fat. CGL1 patients have well preserved mechanical fat (the fat that serves supportive or protective functions and is located in the palms, soles, orbits, scalp and around the joints) and the metabolically active fat (fat that participates in the storage and release of energy and is located at most subcutaneous regions, intermuscular regions, bone marrow, intraabdominal and intrathoracic regions) is absent. CGL2 patients lack both the mechanical and metabolically active fat. The diagnosis thus is evident at birth or immediately afterwards. These infants look very muscular due to the absence of fat. This is an essential criterion for its diagnosis.

Patients also present with acanthosis nigricans (dark velvety pigmentation of the skin) in the axilla, neck or groin, severe insulin resistance, high levels of serum insulin and serum triglycerides and low levels of high-density lipoprotein (HDL) cholesterol. Patients with CGL2 have earlier onset of diabetes and have higher prevalence of mild mental retardation compared to CGL1. These patients also have accelerated growth and advanced bone age during their childhood, and have a voracious appetite. Liver and spleen may be enlarged. Basal metabolic rate of the body may be increased during the childhood. The onset of diabetes is usually during the pubertal years and requires high dose of insulin to control the blood glucose levels.

The other clinical features consist of enlarged hands, feet and prominent mandible (acromegaloid features), increased sweating, umbilical hernia and lytic lesions (bone appear to be eaten-up on X-rays) in long bones of the upper and lower extremities (arms, fore arm, hands, thigh, calf, legs and feet) such as humerus, femur, etc. after puberty. Patients might also have hypertrophic cardiomyopathy (dysfunction of the heart). Females present with enlarged clitoris, increased body hair, absence of or irregular menstrual cycles, and polycystic ovaries (enlarged ovaries).

Genetic basis

AGPAT2 Mutations

Abhimanyu Garg, M.D. and his group identified the gene on the long arm of chromosome 9 (9q34), which when mutated (altered gene) causes CGL1.This gene encodes for the enzyme AGPAT2 (1-acylglycerol-3-phosphate O-acyltransferase 2) that is responsible for the production of an important intermediate in the synthesis of triglycerides or fat. Mutations (alterations) in this gene may cause CGL by inhibiting the fat synthesis and storage in adipocytes (fat cells).

BSCL2 Mutations

Mutations in another gene located on the long arm of chromosome 11 (11q13) called BSCL2 (Berardinelli-Seip Congenital Lipodystrophy 2) also can cause CGL2. The gene product of BSCL2 is a protein, Seipin whose function remains unknown. Therefore how BSCL2 mutations cause CGL remains to be elucidated.

Novel Therapies

Abhimanyu Garg, M.D. and his group carried out a collaborative trial of leptin-replacement therapy in patients with lipodystrophies. Leptin therapy marked reduced the levels of blood glucose and lipids allowing discontinuation of several medications.

* With thanks to Abhimanyu Garg, M.D. for permission to use information.