Lipodystrophies: New Genes, New Insights

Internal Medicine Grand Rounds

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Purpose and Overview:

To illustrate the underlying molecular basis of various types of genetic lipodystrophies and the implications for the diagnosis and management of these syndromes.

Educational Objectives:

1. To identify distinct clinical features of various subtypes of genetic lipodystrophies
2. To understand the role of various lipodystrophy genes in adipocyte biology
3. To understand the challenges in management of metabolic complications in patients with genetic lipodystrophies

Special Interests:

Dr. Garg's group identified deficiency of AGPAT2 enzyme, which is critical for triglyceride and phospholipid biosynthesis, as the cause of congenital generalized lipodystrophy, type 1. His group also linked peroxisome proliferator-activated receptor-γ gene, the key adipocyte differentiation transcription factor, to familial partial lipodystrophy. His team has also identified the second locus for mandibuloacral dysplasia, i.e., zinc metalloproteinase (ZMPSTE24), that is responsible for post translational processing of prelamin A to its mature form lamin A. Recently, Garg and his colleagues uncovered a novel autosomal recessive autoinflammatory syndrome that causes *j*oint contractures, *m*uscle atrophy, *m*icrocytic anemia, and *p*anniculitis-induced lipodystrophy (JMP) and identified the defective gene as proteasome subunit, beta-type 8 (*PSMB8*) which encodes a subunit of the immunoproteasome responsible for generating immunogenic epitopes presented by the major histocompatibility complex (MHC) class I molecules. He demonstrated that patients with generalized lipodystrophy have profound leptin deficiency and proposed that leptin deficiency might contribute to the metabolic complications in the disorder. This led him to initiate a collaborative trial with the NIDDK that demonstrated dramatic improvement in hyperglycemia, dyslipidemia, and fatty liver with leptin therapy.

Lipodystrophies are heterogeneous disorders characterized by selective loss of body fat (1, 2). Some investigators use the term “lipoatrophy” for these disorders. While many patients develop lipodystrophy due to genetic defects, others develop it due to various acquired conditions. These disorders have been reported in the medical literature for more than 100 years. Acquired partial lipodystrophy (APL), which is an autoimmune condition, was the first one to be reported ~125 years ago (3); followed by acquired generalized variety (AGL), an autoimmune or idiopathic condition (4); and only about 59 years ago (5), the phenotype of the first genetic variety, congenital generalized lipodystrophy (CGL), was reported. Interestingly, a new lipodystrophy syndrome was recognized in human immunodeficiency (HIV)-infected patients treated with high-active antiretroviral therapy (HAART) including HIV-1 protease inhibitors about 15 years ago (6), which actually has become the most prevalent type currently among all lipodystrophies.

Patients with lipodystrophies are predisposed to develop insulin resistance and its associated complications such as diabetes mellitus, hypertriglyceridemia, hepatic steatosis, polycystic ovarian disease and acanthosis nigricans. The extent of fat loss determines the severity of metabolic and other complications (1, 2, 7). I have previously discussed lipodystrophy in HIV-infected patients in this forum before. Not much progress has been made in understanding acquired partial or generalized lipodystrophies. However, in the last decade or so, considerable progress has been made in elucidating the molecular genetic bases of many types of inherited lipodystrophies and I will review these syndromes today.

Genetic lipodystrophies can be classified into either autosomal recessive or autosomal dominant disorders. Some patients do develop the syndrome as a result of heterozygous *de novo* mutations.

AUTOSOMAL RECESSIVE LIPODYSTROPHIES

A classification of various subtypes of autosomal recessive lipodystrophies is presented in Table 1. Although all genetic lipodystrophies are rare, some of them are extremely rare. The most severe lipodystrophy syndrome is congenital generalized lipodystrophy (CGL). The other autosomal recessive syndromes include mandibuloacral dysplasia (MAD), autoinflammatory lipodystrophy and familial partial lipodystrophy.

Congenital Generalized Lipodystrophy (Berardinelli-Seip Syndrome)

In 1954, Berardinelli from Rio De Janeiro, Brazil reported two boys (2-year and 6-year-old) with an undiagnosed endocrine-metabolic syndrome presenting with marked hepato-splenomegaly, acromegaloid gigantism, fatty liver and hyperlipidemia (5). In 1959, Seip reported a detailed description of the phenotype of three additional patients and highlighted the onset of generalized lipodystrophy from birth and thus they were recognized as having congenital generalized lipodystrophy (CGL)(8). The diagnosis of CGL is usually made at birth or soon thereafter. However, some patients may have a normal appearance at birth and subsequently lose body fat.

Overall, approximately 300-400 cases of this syndrome have been reported thus far (1, 2, 9). Clusters of cases have been reported from Brazil and Lebanon from regions where there is an increased prevalence of consanguinity (10, 11). Based upon the assumption that only 1/4th of the actual number of cases may be reported in the literature, the estimated prevalence of CGL is about 1 in 10 million (2).

Table 1. Various subtypes of autosomal recessive Lipodystrophies

Type	Subtypes (Gene)	Key Clinical Features	Molecular Basis/ Other Comments
Congenital Generalized Lipodystrophy (CGL)*	CGL1 (*AGPAT2)*	Lack of metabolically-active adipose tissue since birth, lytic bone lesions in appendicular skeleton after puberty	AGPATs are key enzymes required for triglyceride and phospholipids biosynthesis. AGPATs acylate lysophosphatidic acid to form phosphatidic acid. AGPAT2 is highly expressed in adipose tissue.
	CGL2 (*BSCL2)*	Lack of both metabolically-active and mechanical adipose tissue since birth, mild mental retardation, cardiomyopathy	*BSCL2* encodes seipin which may play a role in fusion of small lipid droplets and in adipocyte differentiation.
	CGL3 (*CAV1*)	Single patient with extreme lack of body fat, short stature and vitamin D resistance	Caveolin 1 is an integral component of caveolae, present in abundance on adipocyte membranes. Caveolin 1 binds fatty acids and translocates them to lipid droplets.
	CGL4 (*PTRF)*	Extreme lack of body fat, congenital myopathy, pyloric stenosis, and cardiomyopathy	PTRF (also known as cavin) is involved in biogenesis of caveolae and regulates expression of caveolins 1 and 3.
Mandibuloacral Dysplasia*	Type A (*LMNA*)	Mandibular and clavicular hypoplasia, acro-osteolysis, progeroid features, loss of sc fat from the extremities and trunk	Lamins A and C are nuclear lamina proteins and *LMNA* mutations may disrupt nuclear function resulting in premature cell death in many tissues.
	Type B (*ZMPSTE24*)	Mandibular and clavicular hypoplasia, acro-osteolysis, more generalized loss of fat, premature renal failure, progeroid features, sc calcific nodules	ZMPSTE24 is required for posttranslational processing of carboxy-terminal residues of prelamin A to form lamin A. Accumulation of farnesylated prelamin A may cause cell toxicity and disrupt nuclear function.
Autoinflammatory syndromes	JMP, CANDLE (*PSMB8*)	*J*oint contractures, *M*uscle atrophy, *M*icrocytic anemia and *P*anniculitis-induced lipodystrophy (JMP); *C*hronic *A*typical *N*eutrophilic *D*ermatosis with *L*ipodystrophy and *E*levated Temperature (CANDLE)	*PSMB8* encodes β5i, a catalytic subunit of the immunoproteasomes. Immunoproteasome-mediated proteolysis generates immunogenic epitopes presented by MHC class I molecules. Only about 20 patients reported.
Familial partial lipodystrophy (FPL)	(*CIDEC)*	Single patient with loss of sc fat from the limbs, multilocular, small lipid droplets in adipocytes	CIDEC is a lipid droplet associated protein that inhibits lipolysis and promotes formation of unilocular lipid droplet in adipocytes.
SHORT syndrome	(Unknown)	*S*hort stature, *H*yperextensibility or inguinal hernia, *O*cular depression, *R*ieger anomaly and *T*eething delay	Variable loss of sc fat is observed.
MDP syndrome	(Unknown)	*M*andibular hypoplasia, *D*eafness, *P*rogeroid features, undescended testes and male hypogonadism	Patients usually present with generalized loss of sc fat.
Neonatal progeroid syndrome	(*FBN1*) (Unknown)	Generalized loss of body fat and muscle mass, and progeroid appearance at birth	Some overlapping clinical features of Marfan's syndrome. Molecular basis of other subtypes is unknown.

* Additional rare types for which the genetic basis is not known are not included. AGPAT, 1-acylglycerol-3-phosphate O-acyltransferase; BSCL2, Berardinelli-Seip Congenital lipodystrophy 2; CAV1, caveolin 1; PTRF, polymerase I and transcript release factor; CIDEC, cell death-inducing DNA fragmentation factor a-like effector c; PSMB8, proteasome subunit, beta-type, 8; MHC, major histocompatibility complex; sc, subcutaneous.

Patients with CGL have the appearance of extreme muscularity at birth. This is due to near complete absence of adipose tissue in the body. They are known to grow at an accelerated rate during early childhood and the bone age may be greater than the chronological age at this time (12, 13). They have a markedly increase appetite, and slight enlargement of the hands, feet and mandible, termed acromegaloid features. Nearly all patients have an umbilical hernia or enlargement of the umbilicus (12, 14). Acanthosis nigricans is noted later during childhood or adolescence (12) and can be very severe involving extensive areas of the body (Fig. 1). Besides the typical neck, axillae and groin regions, acanthosis nigricans can also affect the trunk, hands, knees, elbows and ankles. Liver enlargement due to hepatic steatosis is usually noticed during infancy. A few patients develop cirrhosis and its complications later on in life (15, 16) and many patients develop splenic enlargement. In females, mild hirsutism, clitoromegaly, and irregular menstrual periods are common and some present with primary or secondary amenorrhea and polycystic ovaries. Most affected women are unable to conceive, however, a few patients have been reported to have had successful pregnancies. Affected men usually will have normal reproductive ability.

Many patients have been reported to develop focal lytic lesions in the long bones after puberty (13, 16-18). These lytic lesions commonly involve the humerus, femur, radius, ulna, carpal, tarsal or phalangeal bones. The pathogenesis of these lesions may be related to the lack of bone marrow fat and inability to replace hematopoeitic marrow with adipose tissue during childhood and adolescence (16). Some patients have also been reported to have hypertrophic cardiomyopathy and mild mental retardation (19, 20).

CGL is also characterized by high levels of fasting and postprandial insulin, noted very early in life (12). This extreme hyperinsulinemia suggests severe insulin resistance in childhood. Patients also have extreme hypertriglyceridemia which can predispose them to recurrent episodes of acute pancreatitis (14). The levels of high density lipoprotein (HDL) cholesterol also tend to be low. The onset of diabetes usually occurs during the pubertal years; however, diabetes has been reported as early as 6 weeks of life. In some patients, diabetes occurs during the neonatal period and is subsequently followed by a euglycemic period. They again develop diabetes after puberty. We have reported marked amyloidosis of pancreatic islets and β cell atrophy on autopsy of a young adult female with CGL (21). Thus, it appears that prolonged and extreme insulin resistance from birth causes amyloidosis and β cell death due to similar mechanisms involved in patients with type 2 diabetes mellitus. Diabetes is challenging to manage in these patients and may require extremely high doses of insulin to control hyperglycemia (22). Patients are reportedly resistant to ketosis due to endogenous hyperinsulinemia. Since patients with CGL have extreme paucity of body fat, they have markedly low levels of serum adipocytokines such as leptin and adiponectin (23, 24). It is possible that this extreme hypoleptinemia contributes to excessive appetite and metabolic complications in patients with CGL.

At this time there are four distinct genetic varieties of CGL known. However, type 1 and type 2 are the most common subtypes of CGL. The first locus for CGL was discovered by us on chromosome 9q34 using a genome-wide linkage analysis approach (25). We also reported genetic heterogeneity and a possibility of another

locus. Subsequently, the second locus was found on chromosome 11q13 (11). By positional cloning of the 9q34 region, we identified mutations in 1-acylglycerol-3-phosphate-O-acyltransferase 2 (*AGPAT2*) gene in patients with CGL, type 1 (26). Mutations in a new gene called Berardinelli-Seip Congenital Lipodystrophy 2 (*BSCL2*) on chromosome 11q13 were reported by the group of Magre and co-workers (11). Recently, two new genes have been reported to be linked to CGL. A homozygous nonsense mutation in caveolin 1 (*CAV1*) has been reported in a single patient (27) and CGL4 has been linked to mutations in polymerase I and transcript release factor (*PTRF*) (28).

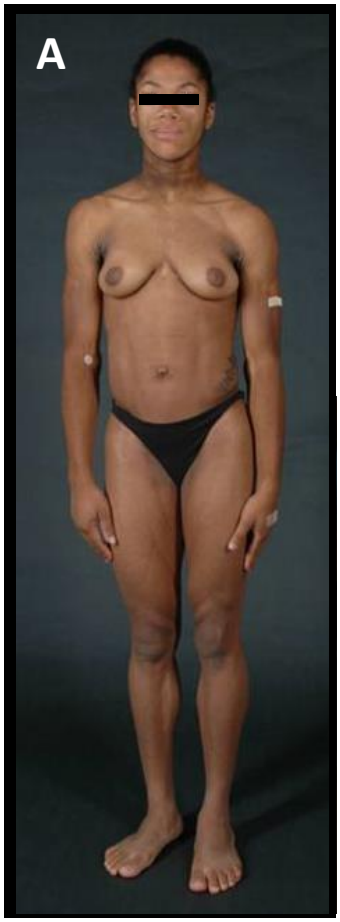


Fig. 1 Anterior view of a 19-year-old female of African-American origin with congenital generalized lipodystrophy type 1, showing generalized lack of fat, extreme muscularity and acromegaloid features. She developed diabetes mellitus at the age of 14 years. Acanthosis nigricans was present in the neck, axillae and groin. She had a homozygous mutation (c.IVS4-2A>G resulting in prematurely truncated protein p.Gln196fsX228) in *AGPAT2*.

CGL Type 1: AGPAT2 mutations

Besides the clinical features mentioned above, patients with CGL type 1 have an increased prevalence of focal lytic lesions in the appendicular skeleton. Metabolically active adipose tissue located in most subcutaneous areas, intra-abdominal and intra-thoracic regions and bone marrow is totally deficient but mechanical adipose tissue which is located in the palms, soles, under the scalp, retro-orbital and peri-articular regions is spared (14, 29).

The AGPATs are key enzymes belonging to the acyltransferase family and play a critical role in the biosynthesis of triglycerides and phospholipids in cells (30, 31). Interestingly, there are 11 isoforms of AGPAT known and each of them is encoded by a different gene (32). The AGPATs acylate lysophosphatidic acid (1-acylglycerol-3-phosphate) to phosphatidic acid (1, 2 diacylglycerol-3-phosphate). The AGPAT2 isoform is highly expressed in the adipose tissue. It is also expressed in the liver and skeletal muscle, but at lower levels. Thus, AGPAT2 deficiency may cause lipodystrophy by lack of triglyceride biosynthesis in the adipocytes or by lack of phospholipid synthesis which may affect adipocyte function. The AGPAT2 protein consists of 278 amino acids and shares two highly conserved motifs, NHX_4D and EGTR. These motifs are critical for enzymatic activity. Besides these well conserved motifs, we have also reported that carboxy-terminal residues may also be important for determination of AGPAT2 enzymatic activity (33). Most of the patients harbor null mutations with no enzymatic activity demonstrable *in vitro*. However, some compound heterozygotes have a null and a missense mutation (with some residual enzymatic activity) and a few have homozygous missense mutations. However, the type of mutation does not determine the severity of lipodystrophy as all the patients have near

complete loss of adipose tissue. Nearly all patients of African origin harbor the founder mutation, c.IVS4-2A>G (p.Gln196fsX228), on one or both alleles (20).

CGL Type 2: BSCL2 mutations

Patients with CGL type 2 display an increased prevalence of cardiomyopathy and mild mental retardation (19, 20). Both metabolically active and mechanical adipose tissue are lacking in CGL, type 2 patients (29). Serum leptin levels are lower in patients with CGL type 2 than type 1, but serum adiponectin levels are higher (24); the reason for this observation is not clear.

The *BSCL2* encodes a 398 amino acid trans-membrane protein called seipin (11, 34). Seipin does not have significant homology to any other known protein. It has a CAAX motif at the carboxy-terminal and a glycosylation site, NVS, at position 88-90. Recent data suggest the role of seipin in lipid droplet formation and in adipocyte differentiation (35, 36). Studies with the seipin homolog in the yeast suggest that it may be playing a role in fusion of lipid droplets. Nearly all mutations reported in patients with CGL2 in BSCL2 are null.

CGL Type 3: Caveolin-1 mutation

This variety has only been reported in a Brazilian girl who had short stature and presumed vitamin D resistance (27). This patient also had hepato-splenomegaly with hepatic steatosis and onset of diabetes at 13 years of age. Additionally, she had acanthosis nigricans and severe hypertriglyceridemia. She had primary amenorrhea at 20 years of age and functional mega-esophagus. The patient had well preserved mechanical and bone marrow fat.

Caveolin-1 is expressed in abundance in caveolae, specialized microdomains on cell membranes of adipocytes (37). Caveolae are known to bring phospholipids and other lipid material from outside to inside the cell and they may contribute this material to lipid droplets. Thus, Caveolin 1 mutation may cause lipodystrophy due to defective lipid droplet formation.

CGL Type 4: PTRF mutations

CGL type 4 due to *PTRF* mutations has been reported in approximately 20 patients (28, 38, 39). These patients have a peculiar phenotype besides having CGL. They manifest developmental delay as well as congenital myopathy with percussion-induced myoedema, pyloric stenosis and atlanto-axial instability (40, 41). Patients with CGL type 4 also have increased levels of creatine kinase in the serum suggestive of myopathy. These patients are prone to developing serious arrhythmias such as catecholaminergic polymorphic ventricular tachycardia, prolonged QT interval, and sudden death (38, 39) . Patients have well preserved mechanical and bone marrow fat. PTRF which is also known as cavin plays a critical role in the biogenesis of caveolae. PTRF regulates the expression of caveolins 1 and 3 and may also contribute to lipid droplet formation (28).

Molecular diagnosis

Patients with CGL should be easily diagnosed at birth or soon thereafter by pediatricians. The two main types of CGL can be distinguished based upon their clinical features. CGL, type 4 has a distinct phenotype of myopathy. Molecular diagnosis at research laboratories is available for confirmation. Molecular diagnosis may be helpful for understanding the risk of having another child with CGL and can also be used for prenatal screening. Besides patients with known genotypes, there are a few patients with CGL who do not have mutations in any of the 4 known loci and thus there may be novel genes to be discovered for CGL.

Differential diagnosis

CGL should be differentiated from acquired generalized lipodystrophy, leprechaunism, atypical Werner syndrome, generalized lipodystrophy due to *LMNA* mutations and neonatal progeroid syndrome.

Mandibuloacral Dysplasia (MAD) associated Lipodystrophy

Mandibuloacral dysplasia (OMIM # 248370) is a rare autosomal recessive disorder reported in about 40 patients so far. It is characterized by hypoplasia of the mandible and clavicles, and acro-osteolysis (resorption of the terminal phalanges) (Fig. 2) (42, 43). Other clinical features include, delayed closure of cranial sutures, joint contractures, mottled cutaneous pigmentation and short stature. Patients also show "progeroid features" such as bird like facies, high-pitched voice, skin atrophy, pigmentation, alopecia, and nail dysplasia. Patients with MAD either have partial loss of subcutaneous fat from the extremities (type A) or more generalized loss of subcutaneous fat involving the face, trunk and extremities (type B). Hyperinsulinemia, insulin resistance, impaired glucose tolerance, diabetes mellitus and hyperlipidemia have been reported but are usually mild to moderate in severity (42).

MAD type A due to LMNA mutations

Following our report characterizing pattern of lipodystrophy in MAD patients to be similar to that seen in patients with familial partial lipodystrophy of the Dunnigan variety, Novelli *et al*. (43) reported a homozygous p.Arg527His mutation in the lamin A/C (*LMNA*) gene in MAD patients with type A (partial) lipodystrophy of Italian origin which appears to be a founder mutation (43).

Lamins belong to the intermediate filament family of proteins and form hetero- or homo-dimeric coiled-coil structures. Lamins play a predominant role in forming the nuclear lamina-- a polymeric structure intercalated between chromatin and the inner nuclear membrane. *LMNA* contains 12 exons and encodes lamins A and C by alternative splicing within exon 10. Lamin A is formed after post-translational processing of prelamin A. Prelamin A has a CAAX motif at its C-terminal which

undergoes farnesylation and then proteolysis by the zinc metalloproteinase (ZMPSTE24) enzyme to form mature lamin A (44, 45). While lamins provide structural integrity to the nuclear envelope, they also interact with chromatin and several other nuclear envelope proteins and these interactions may be important for their biologic role in various tissues.

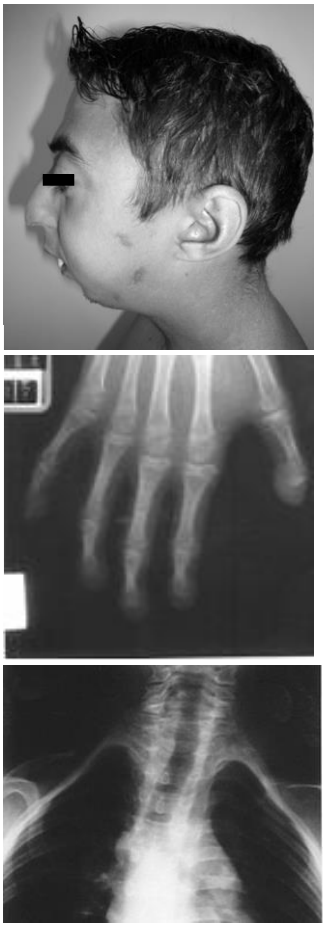


Fig. 2 Clinical features of an 18-year-old patient with mandibuloacral dysplasia, type A. Lateral view of the head and neck shows pointed nose and micrognathia. He had only a few hair on the chin and upper lip. Hair on the eyebrows and eyelids were normal. Roentgenogram of the hand at age 14 years reveals resorption of terminal phalanges consistent with acro-osteolysis and that of the chest reveals clavicular hypoplasia.

So far, a total of 30 patients with MAD due to various *LMNA* mutations have been reported (42, 43, 46, 47). Some patients even develop severe progeroid manifestations, like those seen in progeria patients such as alopecia, loss of eyebrows, delayed sexual maturation and premature loss of teeth (47, 48). Most of the *LMNA* mutations causing MAD are located in the C-terminal region affecting exons 8-10. How these specific *LMNA* mutations cause resorption of bones such as mandible, clavicles and terminal phalanges remains unclear.

MAD type B due to zinc metalloproteinase (ZMPSTE24) mutations

We were the first to report compound heterozygous mutations in *ZMPSTE24* in a Belgian woman with MAD (49). She also had progeroid features and generalized lipodystrophy (49). She died at age 24 years as a result of complications of chronic renal failure due to focal segmental glomerulosclerosis (49). It is suggested that accumulation of prelamin A and/or lack of mature lamin A in the cells may be the underlying mechanism of cellular toxicity. A total of eight patients with this subtype have been reported and most of them have been young children (50, 51). There are no reports of diabetes among them. Patients with *ZMPSTE24* mutations are premature at birth, have early onset of skeletal defects including acro-osteolysis, have more progeroid appearance and develop subcutaneous calcified nodules on the phalanges (49, 50).

Most patients with MAD, type B have compound heterozygous mutations in *ZMPSTE24*, with one of them being a null mutation with no enzyme activity and the other a missense mutation, with some residual enzyme activity. On the other hand, neonates born with two null mutations in *ZMPSTE24* present with a fatal disorder called restrictive dermopathy.

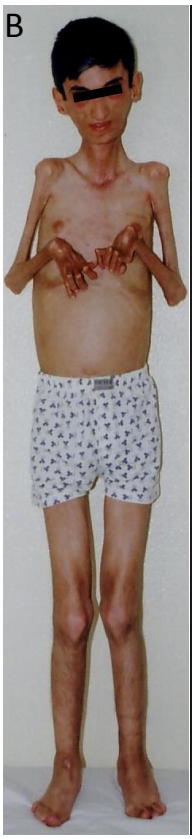
Molecular and Differential Diagnosis

Molecular diagnosis may help predict peculiar clinical features noted in two genetic varieties of MAD. Differential diagnosis includes Hutchinson-Gilford Progeria Syndrome, and atypical Progeroid syndrome (all due to heterozygous mutations in *LMNA*), and other disorders presenting with acro-osteolysis including Hajdu-Cheney (*NOTCH2* mutations), Haim-Munk and Papillon-Lefevre syndromes (both due to Cathepsin C mutations).

_M_andibular hypoplasia, _D_eafness, _P_rogeroid features (MDP) associated lipodystrophy syndrome

We recently reported this novel syndrome with *m*andibular hypoplasia, *d*eafness, *p*rogeroid features (MDP) -associated lipodystrophy in seven patients (104). None of them had any mutations in *LMNA* or *ZMPSTE24*. As compared to MAD patients, they showed distinct characteristics such as sensorineural hearing loss, and absence of clavicular hypoplasia and acro-osteolysis. All the males with MDP had undescended testes and hypogonadism. One adult female showed lack of breast development. Two of the seven patients had diabetes mellitus. The molecular basis of MDP syndrome remains to be elucidated.

Auto-inflammatory Lipodystrophy Syndrome



Recently, we (52) reported an autosomal recessive, autoinflammatory, *J*oint contractures, *M*uscle atrophy, *M*icrocytic anemia and *P*anniculitis-induced lipodystrophy (JMP) syndrome in two pedigrees where affected patients had onset of progressive panniculitis-induced lipodystrophy during childhood (Fig. 3). Similar patients had been previously reported from Japan (53, 54). Additional clinical features include intermittent fever, hypergammaglobulinemia, elevated erythrocyte sedimentation rate, hepatosplenomegaly and calcification of basal ganglia. Two groups recently reported five patients with Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) syndrome who have some overlapping manifestations such as recurrent fever and annular violaceous plaques during infancy which result in lipodystrophy of the face and upper limbs (55, 56).

Fig. 3 Anterior view of patient autoinflammatory lipodystrophy (JMP syndrome) showing marked loss of sc fat from the face, neck, chest and upper extremities. The loss of sc fat is less evident from the abdomen and lower extremities. There is also loss of muscle mass from the upper extremities. Contractures of the upper extremities with flexion contracture at the elbows and wrists and contractures of the hands are seen. The patient has mild gynecomastia. Patient has no loss of scalp hair (52).

We reported a homozygous, missense, loss of function, mutation in proteasome subunit, beta-type, 8 (*PSMB8*) gene in affected patients

from both our pedigrees (57). *PSMB8* encodes the β5i subunit of the immunoproteasome (58). Immunoproteasomes are responsible for proteolysis of antigens presented by major histocompatibility complex (MHC) class I molecules and result in generation of immunogenic epitopes. The mutation in *PSMB8* may trigger autoinflammatory response which results in panniculitis and other clinical manifestations. A total of 20 patients (2-51 years old) have been reported to harbor *PSMB8* mutations but only one of these patients had diabetes (57, 59-61). All of these patients represent variable manifestations of the same syndrome.

Short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Reiger anomaly and teething delay (SHORT) Syndrome

A total of 30 patients have been reported with SHORT syndrome. The pedigrees reveal both autosomal recessive (62, 63) and dominant (64-66) modes of transmission (62-64). Reiger anomaly consists of eye abnormalities such as iris hypoplasia, Schwalbe ring, iridocorneal synechiae, micro- or megalo-cornea and dental anomalies such as hypodontia, microdontia, enamel hypoplasia and atypical teeth. Other clinical features include intrauterine growth retardation, failure to thrive, delayed speech development, small head circumference, bilateral clinodactyly and sensorineural hearing loss. Different patterns of fat loss have been reported. In many patients, lipodystrophy affects the face, upper extremities and sometimes the trunk, with relative sparing of the lower extremities. Others had lipodystrophy affecting only the face, gluteal region and elbows (65, 66). Diabetes occurs as early as the second and third decade of life. The pathogenesis of diabetes mellitus remains unclear. The genetic basis remains unknown.

Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)

This is an autosomal recessive syndrome with a total of approximately 25 reported cases (67-70). Newborns with this syndrome have a triangular, old-looking face with relatively large skull (progeroid appearance), prominent veins on the scalp, sparse scalp hair, large anterior fontanelle and generalized lipodystrophy. However, subcutaneous fat in the sacral and gluteal areas is spared (69-71). Approximately, half of the patients die before the age of 6 years but patients surviving up to the age of 16 years have been reported (69, 71-73). Recently, two patients also manifesting clinical features of Marfan's syndrome were reported to harbor *de novo* heterozygous mutations in fibrillin 1 (*FBN1*) gene (74, 75). No patient has been reported to develop diabetes.

Familial Partial Lipodystrophy (FPL) due to *CIDEC* mutation:

A 19-year-old Ecuadorian girl with autosomal recessive FPL has been reported to harbor a homozygous missense mutation in cell death-inducing DNA fragmentation factor a-like effector c (*CIDEC*) (76). She developed diabetic ketoacidosis at age 14 and also had hypertriglyceridemia and hypertension. On biopsy of subcutaneous fat

multilocular, small lipid droplets were reported in adipocytes consistent with the findings in the knock out mouse model (76, 77).

AUTOSOMAL DOMINANT LIPODYSTROPHIES

A classification of various subtypes of autosomal dominant lipodystrophies is presented in Table 2. The most prevalent are the familial partial lipodystrophies.

Table 2. Various subtypes of autosomal dominant lipodystrophies

Type	Subtype	Key Clinical Feature	Molecular Basis/ Other Comments
Familial Partial Lipodystrophy (FPL)	FPLD1, Kobberling (unknown)	Loss of sc fat from the extremities	Phenotype not well characterized
	FPLD2, Dunnigan (*LMNA*)	Loss of sc fat from the extremities and trunk (sparing the face and neck) at puberty	Lamins A and C are nuclear lamina proteins and specific mutations may disrupt nuclear function resulting in premature death of adipocytes.
	FPLD3 *(PPARG)*	Loss of sc fat from the extremities, especially from distal regions, some patients have severe hypertension	PPARγ is a critical transcription factor required for adipogenesis. Dominant negative PPARγ mutations may inhibit adipocyte differentiation.
	FPLD4 (*AKT2*)	Single family reported with loss of sc fat from the extremities	AKT2, also known as protein kinase B, is involved in adipocyte differentiation and downstream insulin receptor signaling.
	FPLD5 (*PLIN1*)	Loss of sc fat from the extremities with small adipocytes and increased fibrosis of adipose tissue	Perilipin 1 is an integral component of lipid droplet membranes and is essential for lipid storage and hormone regulated lipolysis.
Atypical progeroid syndrome	(*LMNA*)	Variable loss of sc fat, progeroid features	Different heterozygous mostly *de novo* mutations in *LMNA* cause nuclear dysfunction.
Hutchinson-Gilford Progeria	(*LMNA*)	Generalized loss of sc fat, progeroid features	Specific *de novo LMNA* mutations induce abnormal splicing and accumulation of truncated farnesylated prelamin A.
SHORT syndrome	Unknown	See above	Molecular basis is unknown.

LMNA, lamin A/C ; PLIN1, perilipin 1 ; AKT2, v-AKT murine thymoma oncogene homolog 2; PPARG, peroxisome proliferator-activated receptor γ.

Familial Partial Lipodystrophies (FPL)

The characteristic clinical feature of patients with familial partial lipodystrophies is the loss of body fat from the upper and lower extremities as well as in some patients from the truncal region (78, 79). Most of the patients follow an autosomal dominant inheritance pattern. The phenotype can be easily recognized in affected women; however, recognition of men affected with FPL is difficult because even some normal healthy men also appear very muscular and have markedly low subcutaneous fat. Therefore, most of the ascertainment of affected patients and pedigrees has been through female probands. The diagnosis should be suspected in patients who show signs of insulin resistance early in life manifested by acanthosis nigricans or polycystic ovarian syndrome and early onset of diabetes and severe hypertriglyceridemia. Patients who have these manifestations but do not have generalized obesity should be suspected to have FPL and physicians should examine for fat loss from the extremities, particularly from the gluteal region. Many patients gain fat in non-lipodystrophic regions such as the face, under the chin, posteriorly in the neck resulting in a dorso-cervical

hump and in the intra-abdominal region. Some women also gain fat in the perineal region, especially in the labia majora and pubic region. Several distinct subtypes of FPL have been reported and the molecular genetic basis of 4 distinct subtypes is known.

Type 1 Kobberling variety

After the original description by Dunnigan (78), Kobberling and co-workers (79) from Germany reported a phenotype of FPL which was distinct from that reported earlier by Dunnigan. The Kobberling variety is less common and has been reported in only two small pedigrees and four sporadic cases (79-81). The age of onset of lipodystrophy and the mode of inheritance are not clear. On the basis of clinical findings, the loss of adipose tissue in the Kobberling variety is restricted to extremities only. Patients have normal amounts of fat in the face area and may have normal, or even excess, subcutaneous fat in the truncal area. The genetic basis for this particular variety is unknown.

Type 2 Dunnigan variety (FPLD: LMNA mutations)

This lipodystrophy was initially described in an abstract form by Ozer and co-workers (82) who reported a 52-year-old woman and several members of her family with “fat neck syndrome” but loss of subcutaneous fat from the limbs. All affected patients had hypertriglyceridemia, and some had impaired glucose tolerance and diabetes. Subsequently, Dunnigan and co-workers (78) provided a detailed phenotypic description of two families with an autosomal dominant variety of FPL. Initial reports of this syndrome were restricted to the description of affected females only possibly because recognition of affected males was difficult. It was also thought that they may have an x-linked dominant inheritance pattern with lethality in hemizygous males (80). Ascertainment of additional pedigrees subsequently showed that it clearly followed an autosomal dominant inheritance pattern (83). Since the original description, approximately 500 patients may have been reported with FPL. Most of them are of European origin but other ethnicities have been reported to have FPL, such as Asian Indians and African-American patients.

The onset of FPLD occurs in late childhood or at puberty. Therefore, children at birth have normal body fat distribution. Even as young children, their appearance is completely normal but during late childhood or with onset of puberty patients start losing subcutaneous fat in the upper and lower extremities including the gluteal region (Fig. 4). At the same time, they start gaining subcutaneous fat in non-lipodystrophic regions, such as the face, neck and in the intra-abdominal region. Acanthosis nigricans also appears at the time of puberty and approximately 1/3rd of women affected with FPLD have irregular periods, oligo-amenorrhea, and hirsutism suggestive of polycystic ovarian syndrome (84). Characterization of the phenotype by whole body magnetic resonance imaging has revealed marked loss of subcutaneous fat from the extremities but preservation of inter-muscular fat present in between the muscle fascia (85). Excess accumulation of fat is seen in the intra-abdominal and intra-thoracic region as well. Some patients develop a round face, dorsal cervical hump, double chin and

enlargement of supra-clavicular fat pads, and these patients are mistaken as having Cushing's syndrome. Although the data are limited, it appears that the affected women are more severely affected by metabolic derangements than the affected males (84, 86). The prevalence of diabetes in affected women is approximately 50%, as compared to 20% in the affected men (84). Women also show extreme hypertriglyceridemia and low levels of HDL cholesterol and increased prevalence of coronary heart disease.

Diabetes usually develops after the second decade of life and the risk factors for development of diabetes have been found to be multiparity and excess fat deposition in the non-lipodystrophic regions such as the chin. Autopsy study in a patient revealed severe amyloidosis of pancreatic islets which may be related to the onset of hyperglycemia and diabetes in patients with FPLD (87). Some patients with FPLD also develop cardiomyopathies which manifest both as cardiac conduction system disturbances resulting in atrial fibrillation requiring pacemaker implantation and premature congestive heart failure requiring cardiac transplantation (88, 89).

Using a genome wide linkage analysis approach, we reported the FPLD locus on chromosome 1q21-22 in 5 large informative pedigrees (83). This was the first report of linkage of a lipodystrophy locus. Subsequently, Cao and Hegele (90) screened for candidate genes in the chromosome 1q21 region and reported a single missense mutation, p.Arg482Gln, in lamin A/C (*LMNA*) gene in a Canadian pedigree. Since then, several missense mutations in *LMNA* have been reported in patients with FPLD, most of them affecting the C-terminal amino acids (91-93).

Fig. 4 A 28-year-old Hispanic woman with familial partial lipodystrophy, Dunnigan variety (FPL, Type 2) due to heterozygous missense mutation in the *LMNA* gene. She had loss of fat from the extremities and trunk beginning at puberty and had excess fat accumulation in the face, neck and perineal region. She had acanthosis nigricans in the axillae and groins.

Mutations in *LMNA* interestingly have also been reported in various other disorders such as idiopathic cardiomyopathy, muscular dystrophies, Hutchison-Gilford Progeria syndrome, Charcot-Marie Tooth neuropathy, mandibuloacral dysplasia and atypical progeroid syndrome (93). Some patients with FPLD harboring *LMNA* mutations show features of overlap syndrome and have some mild muscular dystrophy as well as cardiac conduction system disturbances (88, 89). Thus, we have proposed that *LMNA* mutations may also cause a multisystem dystrophy syndrome which can affect various tissues including adipose, cardiac, skeletal muscle, nerve, cutaneous and skeletal tissue (88).

However, how specific mutations in *LMNA* cause adipocyte loss from mainly extremities remains unknown. It is hypothesized that disruption of interactions of lamins A and C with chromatin or other nuclear lamina proteins during the cell division may lead to premature cell death or apoptosis of adipocytes. The accumulation of excess fat in non-lipodystrophic regions may be a secondary phenomenon.

Most of the missense mutations in FPLD accumulate or affect exon 8 of *LMNA* which encodes for the globular C-terminal (tail) portion of the protein. Particularly, the Arginine residue at position 482 seems to be a hot spot and about 75% of the patients with FPLD have a substitution of this residue either to tryptophan, glutamine or leucine (93). Some patients who have mutations in exon 11, which can only affect lamin A and not lamin C, seem to have a milder, atypical FPLD (94). More importantly, patients who have mutations in exon 1 or nearby exons affecting the amino terminal residues have associated cardiomyopathy (88, 89). Some of these patients also show evidence of mild muscular dystrophy with slightly increased serum creatine kinase levels. In some families, these mutations lead to severe congestive heart failure in the 3rd decade resulting in a need for cardiac transplantation.

By clinical examination it is difficult to diagnose affected men as well as pre-pubertal children with FPLD. Therefore, molecular diagnosis may be helpful in characterizing these patients. Furthermore, genotyping for mutations which are also associated with cardiomyopathies may be particularly important for predicting prognosis.

Type 3: FPL associated with PPARG mutations

Using a candidate gene approach, we identified a heterozygous missense mutation, p.Arg397Cys, in the *PPARG* in a 64-year-old woman who presented with diabetes, hypertriglyceridemia, hypertension and hirsutism (95). She also had lipodystrophy of the face and extremities that was noticed much later in life. Since then, approximately 30 patients with FPL due to *PPARG* mutations have been reported (96). These patients manifest insulin resistance with diabetes, hypertension and hypertriglyceridemia. Hypertension in some patients has been reported to be severe. The age of onset of this variety of lipodystrophy is not precisely known, but may range from second decade or later. Also the pattern of progression of fat loss is not very clear. Patients have more fat loss from the distal extremities than from the proximal extremities. Patients have been reported to have variable loss of fat from the face, and some patients have normal or increased fat on the face. Given the role of PPARγ as a transcription factor in adipogenesis and adipocyte differentiation, mutations in *PPARG* may result in lipodystrophy due to defective differentiation of adipocytes. *PPARG* is highly expressed in adipose tissue, however, why patients with *PPARG* mutations develop lipodystrophy of the extremities and not other adipose tissue depots is not very clear.

Type 4: FPL associated PLIN1 mutation

Recently, Gandotra and co-workers (97) reported two heterozygous frameshift mutations in *PLIN1* in five patients from three families with FPL of European origin. All of them had fatty liver, hypertriglyceridemia and hyperinsulinemia. Three of them had diabetes and four of them had reduced levels of HDL cholesterol. Lipodystrophy was most striking in the lower limbs and femoro-gluteal depots. Acanthosis nigricans was present in all probands and two of them also had a cushingoid appearance. The

investigators reported the histopathology of subcutaneous adipose tissue from four patients with *PLIN1* mutations revealing reduced size of adipocytes and increased macrophage infiltration and adipose tissue fibrosis. Upon over expression of *PLIN1* in 3T3-L1 pre-adipocytes, the investigators noted that mutant PLIN1 resulted in smaller lipid droplets compared to the wild type PLIN1 (97). Perilipin is the most abundant protein coating lipid droplets in adipocytes (98). It is considered to be essential for formation and maturation of lipid droplets and storage of triglycerides as well as release of fatty acids from these lipid droplets. Recent information suggests that mutant forms of PLIN1 fail to bind to AB-hydrolase containing 5, which results in constitutive co-activation of adipose triglyceride lipase and increased basal lipolysis (99).

Type 5: FPL associated with AKT2 mutations

George et al. (100) reported a heterozygous missense mutation, p.Arg274His, in *AKT2* in four subjects from a family who presented with insulin resistance and diabetes mellitus. The proband, a 35-year-old Caucasian female, developed diabetes at age 30, whereas her affected mother and grandmother developed diabetes during their late thirties. A maternal uncle, a middle-aged person, had no diabetes but had hyperinsulinemia. Three of the four affected subjects had hypertension. The proband also had loss of subcutaneous fat from the extremities (Stephen O'Rahilly personal communication). However, the precise pattern of subcutaneous fat loss is not clear. AKT2 is a phosphoinositide-dependent serine/threonine kinase and is also known as protein kinase B (PKB). AKT2 is predominantly expressed in insulin sensitive tissues. Overexpression of the mutant form, p.Arg274His, in 3T3-L1 mouse preadipocytes, resulted in markedly reduced lipid accumulation. Previously, a knock-out mouse model has shown features of lipodystrophy, insulin resistance and diabetes with increasing age (101). Thus, taken together, lipodystrophy in patients with *AKT2* mutations may be related to reduced adipocyte differentiation and may be likely due to dysfunctional insulin signaling at the post-receptor level.

Other Types of FPL

The four known FPL genes are not able to explain the genetic basis of all the patients with FPL and there is likelihood of additional loci (95, 102). In depth characterization of the clinical phenotype related to the pattern of fat loss in FPL patients with mutations in different genes may be helpful in identification of different phenotypes without resorting to molecular diagnosis.

Differential Diagnosis

FPL should be differentiated from conditions such as Cushing's syndrome, truncal obesity, multiple symmetric lipomatosis, acquired generalized lipodystrophy as well as highly active anti-retroviral therapy induced lipodystrophy in HIV-infected patients.

Atypical progeroid syndrome due to *LMNA* mutations

About 30 patients have been reported to have partial or generalized lipodystrophy, insulin resistant diabetes and progeroid features with missense mutations in *LMNA* gene (103). Additional clinical features include mottling, pigmentations and sclerosis of skin, liver steatosis, cardiomyopathy, short stature, cardiac valvular abnormalities and deafness. Particularly striking is the lack of breast tissue in many females. Some women also develop premature ovarian failure.

Hutchinson-Gilford Progeria Syndrome (HGPS)

Patients with HGPS appear normal at birth but develop features of early aging during neonatal period or early childhood (104-106). These features include, severe alopecia, graying of hair, micrognathia, beaked nose, shrill voice, and extensive wrinkling of the skin due to loss of underlying adipose tissue, poor sexual development, joint contractures and severe atherosclerosis (104). Many of them die between the ages of 6 to 20 years. Most of them have synonymous *de novo* heterozygous *LMNA* mutation p.Gly608Gly (107). This mutation presents a cryptic splice site resulting in a mutant truncated form of prelamin A with 50 carboxy-terminal amino acids deleted. Occasional patients have other missense *LMNA* mutations (107-109). Patients develop severe lipodystrophy with increasing age (106). Interestingly, diabetes among HGPS patients is rare (105, 106).

Summary

Progress in understanding the molecular genetic bases of genetic lipodystrophies has revealed that these disorders can be due to mutations in various genes involved in adipose tissue development, differentiation and death (Fig. 5). Further, mutations in many proteins involved in the storage of triglycerides in lipid droplets in adipocytes may also result in lipodystrophies. Finally, disruption of autoinflammatory pathways may also result in loss of adipocytes due to panniculitis.

DIAGNOSIS and PROGNOSIS

While the phenotype of CGL is so striking that the diagnosis should be apparent at birth, the diagnosis can be delayed in children with FPL or atypical progeroid syndrome for several years till they see a specialist. Lipodystrophies should be considered in differential diagnosis of patients presenting with early diabetes, severe hypertriglyceridemia, hepatic steatosis, hepato-splenomegaly, acanthosis nigricans and polycystic ovarian syndrome. A thorough physical examination of “lean” patients with these metabolic complications to look for evidence of fat loss should clinch the diagnosis. It is especially important to examine the extremities and hips for signs of fat loss and muscular prominence. Some patients may present with excess sc fat

deposition in various anatomic regions and may resemble patients with Cushing's syndrome and truncal obesity. In those suspected to have genetic lipodystrophies, an in depth pedigree analysis should be conducted to understand the mode of inheritance. Parents should be probed for any consanguinity. Careful examination of the male first degree relatives can sometimes reveal previously undiagnosed FPL.

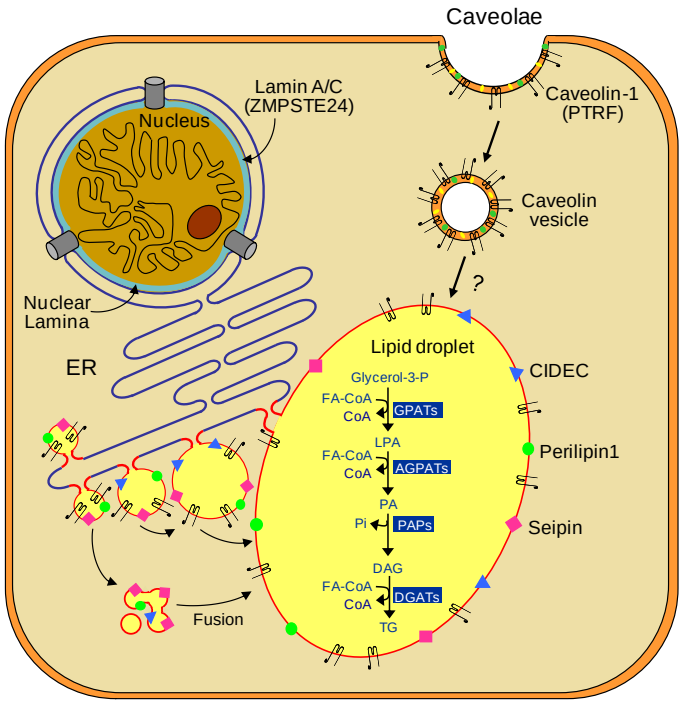


Fig. 5. Lipid droplet formation in adipocytes. Lipid droplets (LD) are organelles that store triglycerides (TG) intracellularly. In the adipocytes, they form as budding vesicles at the endoplasmic reticulum (ER) that fuse together to form one large LD. Many proteins, such as CIDEC (shown in *blue triangles*), seipin (*pink squares*), and perilipin 1 (*green circles*) are present on the LD membrane. CIDEC and seipin may be involved in fusion of LDs to form a larger LD, whereas perilipin 1 is essential for lipid storage and hormone-mediated lipolysis. Caveolae are formed from lipid rafts on the cell surface, which include cholesterol (*yellow symbols*), glycosphingolipids (*green symbols*), and caveolin-1 (*black hairpin-like symbols*). Endocytosis of caveolae forms caveolin vesicles that may directly merge with lipid droplets and thus translocating fatty acids to LDs. PTRF controls expression of caveolin 1 and 3 (data not shown). The classical and alternative pathways involved in the biosynthesis of TG are shown inside the lipid droplet. In the adipose tissue, TG synthesis requires glycerol-3-phosphate as the initial substrate (classical pathway), whereas in the small intestine, synthesis of TG can occur via an alternative pathway using monoacylglycerol (MAG) as the initial substrate. Acylation of glycerol-3-phosphate using fatty acyl coenzyme A (FA-CoA) at the sn-1 position is catalyzed by glycerol-3-phosphate acyltransferases (GPATs), resulting in the formation of 1-acylglycerol-3-phosphate or lysophosphatidic acid (LPA). LPA is then acylated at the sn-2 position by AGPATs to yield phosphatidic acid (PA). Removal of phosphate group from PA by PA phosphatases (PAP) produces diacylglycerol (DAG). Further acylation of DAG at the sn-3 position by diacylglycerol acyltransferases (DGATs) finally produces TG. Lamin A/C are integral components of nuclear lamina (shown in *blue color*) and interact with nuclear membrane proteins as well as chromatin. Zinc metalloproteinase (ZMPSTE24) is critical for posttranslational processing of prelamin A to its mature form, lamin A. [Modified from A. Garg and A. K. Agarwal: Caveolin-1, a new locus for human lipodystrophy. *J Clin Endocrinol Metab* 93:1183–1185, 2008. © The Endocrine Society. And from A. Garg and A. K. Agarwal: Lipodystrophies: disorders of adipose tissue biology. *Biochem Biophys Acta* 1791:507–513, 2009.

The diagnosis of various types of lipodystrophies is mainly clinical. Laboratory tests can only provide additional supportive evidence. All patients except those with localized lipodystrophy should be tested for glucose intolerance, serum lipids, liver function tests and hyperuricemia. Measurement of serum leptin does not help diagnostically but may predict response to investigational metreleptin replacement therapy. Skeletal surveys may reveal lytic bone lesions in appendicular skeleton in CGL patients and various skeletal defects in MAD patients. A deep skin biopsy clinches the diagnosis of panniculitis. Electrocardiography, holter monitoring, echocardiography and stress test should be conducted for patients suspected of having cardiomyopathy or coronary heart disease.

Beyond physical examination, skinfold thickness measurement, dual energy X-ray absorptiometry and a whole body T-1 weighted magnetic resonance imaging can provide information on the pattern of fat loss. Genetic testing, including prenatal diagnosis is available for *AGPAT2*, *BSCL2*, *LMNA*, *ZMPSTE24* and *PPARG* in clinical laboratories and some research laboratories including our own perform genetic testing of all loci.

Patients with generalized lipodystrophies are predisposed to developing acute pancreatitis, cirrhosis, end stage diabetic renal disease requiring renal transplantation, and blindness due to diabetic retinopathy. Many patients with FPL die of coronary heart disease or cardiomyopathy and rhythm disturbances (86, 88, 89). Some patients with MAD die during childhood of unknown reasons and while some others die during early adulthood due to complications of renal failure due to focal segmental glomerulosclerosis (50, 51). Sudden death has been reported during childhood in CGL, type 4 likely due to arrhythmias (39).

MANAGEMENT

Treatment of lipodystrophies is quite challenging. Proper counseling of the parents as far pathogenesis and expected course of the type of lipodystrophy is critical for allaying stress and psychological sequelae in children affected with lipodystrophies. Parents should provide support to affected children to help them adjust among their friends and classmates. Since reversal of the lost adipose tissue is not possible, cosmetic surgery to improve appearance, and management of metabolic complications are the only therapeutic options. Autologous adipose tissue transplantation or implantation of dermal fillers can improve facial appearance. Unwanted excess adipose tissue from the chin, buffalo hump and vulvar region can be surgically excised or removed by liposuction. CGL patients can undergo reconstructive facial surgery including mandibular resection.

No controlled clinical trials have been conducted to help guide drug therapy for metabolic complications. For severe hypertriglyceridemia, fibrates and fish oil should be used and may be combined with statins in some patients. Metformin should be the first line therapy for diabetes. There is no hard evidence to show that thiazolidinediones can improve fat deposition in lipodystrophic regions (110). Instead, in patients with partial lipodystrophies, they can potentially increase unwanted fat deposition in nonlipodystrophic regions. Whether thiazolidinediones should be the choice of therapy in FPL patients with *PPARG* mutations is not clear (111). Since many patients with lipodystrophies have extreme insulin resistance, they may require high doses of insulin, including administration of U-500 insulin (500 units of insulin per mL).

Diabetes control in patients with lipodystrophies can be challenging. A multi pronged strategy should be used including diet, physical activity and drug therapy. Reduction of energy intake and increased physical activity is important in patients with FPL to avoid excess fat deposition in nonlipodystrophic regions. Many patients with FPL have increased risk of coronary heart disease and they should limit intake of saturated and trans-unsaturated fats and dietary cholesterol. Patients presenting with acute pancreatitis and extreme chylomicronemia should be advised to consume an extremely

low fat diet. However, whether such diet will be beneficial in the long term to reduce hepatic steatosis, serum triglycerides and improve glycemic control remains unclear. Three FPL patients have been reported to have had marked improvement in diabetes control and dyslipidemia following roux-en-y gastric bypass surgery (112-114).

Controlling excessive hunger in children with generalized lipodystrophy is extremely difficult. Metreleptin is an investigational therapy and may be able to suppress appetite (22, 115). However, enough energy should be provided for proper growth and development. Subcutaneous metreleptin replacement in low doses has been reported to dramatically improve diabetes control, hepatic steatosis and hypertriglyceridemia in severely hypoleptinemic patients with generalized lipodystrophies (22, 115-117). Metreleptin replacement, however, is only modestly efficacious in patients with FPL (22, 115, 118, 119). Metreleptin therapy remains investigational and is not yet approved by the Food and Drug Administration of the U.S.

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