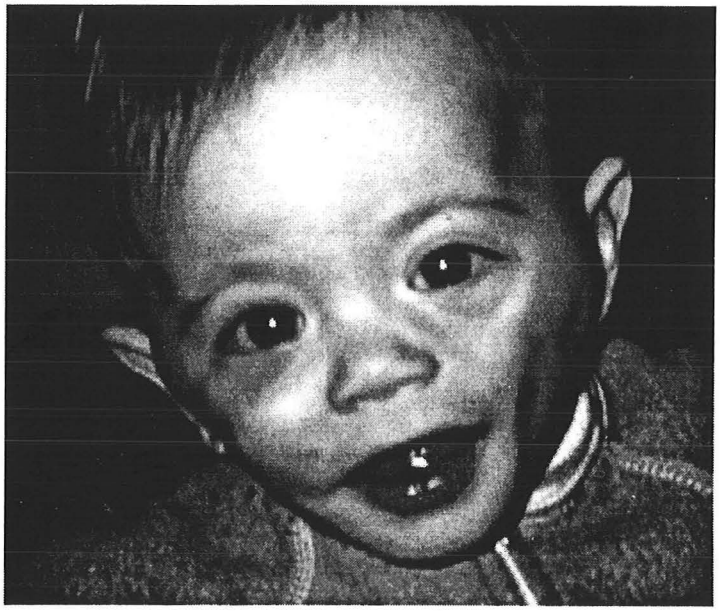
Medical Grand Rounds
September 3, 1998

Lipodystrophies:
Old syndromes, new insights



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Special Interests:
Lipodystrophies and other disorders of adipose tissue
Lipoprotein disorders in diabetes
Nutrition in patients with diabetes
Regional obesity, insulin resistance and syndrome 'x'

Cover illustration: 1 year-old boy developing acquired generalized lipodystrophy.

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INTRODUCTION

The lipodystrophies are a heterogeneous group of adipose tissue disorders characterized by loss of fat from various parts of the body (1). Fat loss can range from small areas causing well-demarcated subcutaneous (sc) depressed areas or indentations as seen in localized lipodystrophies to near complete absence of adipose tissue seen in patients with congenital generalized lipodystrophy. The extent of fat loss may determine the severity of metabolic complications such as insulin resistance, diabetes mellitus, dyslipidemia and hypertension. For example, some patients may have only cosmetic problems, but others may also have severe derangements in intermediary metabolism with hepatomegaly and eventual liver failure.

The syndromes of lipodystrophies were originally described in the medical literature towards the end of 19th Century and early 20th Century (Table 1, 2-10).

Table 1. Historical milestones in syndromes of lipodystrophy

1885	Mitchell	Acquired partial lipodystrophy (APL)
1907	Barraquer	
1911	Simons	
1928	Zeigler	Acquired generalized lipodystrophy (AGL)
1946	Lawrence	
1954	Berardinelli	Congenital generalized lipodystrophy (CGL)
1959	Seip	
1973	Ozer	Familial partial lipodystrophy, Dunnigan variety (FPLD)
1974	Dunnigan	

Since these original descriptions, more than 500 patients with various types of lipodystrophies have been reported in the scientific literature. Despite these reports, there is considerable confusion in the nomenclature because of lack of well-defined diagnostic criteria and poor understanding of the etiology and pathogenesis of these disorders. The following classification, given in Table 2, is based on the current understanding and is used in my presentation. Table 3 lists various disorders that should be differentiated from different types of lipodystrophies. Clinical descriptions of some of these disorders have included references to lipodystrophies; however, systematic studies have not been performed to document typical patterns of loss of adipose tissue. Therefore, these disorders are listed separately and will be discussed later.

Table 2. Classification of Lipodystrophies:

I. Familial or Genetic Forms
   1. Congenital generalized lipodystrophy (CGL; Berardinelli-Seip Syndrome)
   2. Familial partial lipodystrophy (FPL)
      a. Dunnigan variety (FPLD)
      b. Kobberling variety
      c. Other types

II. Acquired Forms
   1. Acquired generalized lipodystrophy (AGL; Lawrence syndrome)
   2. Acquired partial lipodystrophy (APL; Barraquer-Simons syndrome, Cephalothoracic lipodystrophy, Progressive lipodystrophy)
   3. Localized lipodystrophies
   4. HIV-1 protease inhibitors-induced lipodystrophy

Table 3. Differential Diagnosis of lipodystrophies

1. SHORT syndrome
2. Mandibuloacral dysplasia
3. Werner's syndrome (Progeria)
4. Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)
5. Severe weight loss (malnutrition, famine, anorexia nervosa, malabsorption syndromes, cachexia, thyrotoxicosis, adrenocortical insufficiency)
6. Multiple symmetric lipomatosis (Madelung's disease, Launois-Bensaude syndrome)
7. Cushing's syndrome

FAMILIAL LIPODYSTROPHIES

Congenital Generalized Lipodystrophy (CGL)

CGL, also known as Berardinelli-Seip syndrome (OMIM # 269700), is an extremely rare autosomal recessive disorder of adipose tissue (7,8). Less than 100 cases with CGL have been described in the literature. Assuming that the literature reports reflect only 25% of the true prevalence, a conservative estimate of its prevalence may be 1 in 12.5 million.

a. *Clinical Features*:

There is a near complete absence of adipose tissue from birth, with acanthosis nigricans, severe insulin resistance, marked hyperinsulinemia and hypertriglyceridemia and onset of diabetes mellitus during pubertal years (1,11). Other features include hepatosplenomegaly, acromegaloid appearance (enlarged hands, feet and prominent mandible), umbilical hernia, and in women, clitoromegaly, hirsutism, oligo/amenorrhea and polycystic ovaries. Postpubertal patients may have lytic bone lesions confined to appendicular skeleton (12-15).

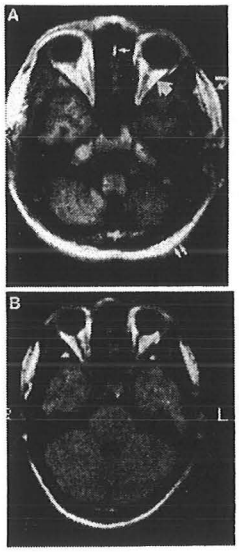


Fig. 1 A. Axial MRI through orbits in a patient with CGL showing presence of fat in the orbits (arrow head), temporal region (curved arrow), crista galli (small arrow), and subcutaneous area of scalp (double arrows). B. Similar image from a normal volunteer showing normal distribution of fat in the orbits, temporal region, and subcutaneous area of scalp.

Using whole body magnetic resonance imaging (MRI), we have previously shown that patients with CGL have a characteristic distribution of adipose tissue (Figs. 1-3; 16). There is complete absence of adipose tissue in intraabdominal, mesenteric, retroperitoneal, particularly perirenal, peripancreatic and periadrenal areas and epicardial areas. In addition, bone-marrow fat is absent (16). On the other hand, normal amount of adipose tissue is present in orbits, crista galli, buccal region, tongue, palm and soles, scalp, perineum, vulva, pericalyceal region of kidney, peri-articular regions and epidural area. This peculiar adipose tissue distribution suggests that the "metabolically-active" adipose tissue is almost completely absent whereas "mechanical" adipose tissue is present in normal amounts in CGL. This characteristic distribution of adipose tissue on the MRI studies in three women with CGL was confirmed on autopsy of

one of them (17). More recently, MRI studies in two siblings with CGL, a 16-year-old girl and a 14-year-old boy, have confirmed the characteristic adipose tissue distribution in both sexes. Therefore, MRI studies can provide unequivocal confirmation of phenotype in CGL subjects and differentiate them from acquired generalized lipodystrophy.

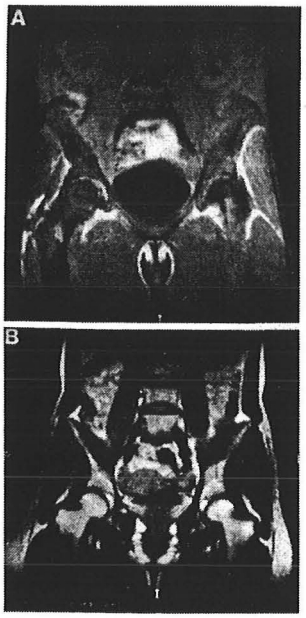


Fig. 2 A. Coronal MRI through hip joints in a patient with CGL, showing absence of perinephric and retroperitoneal fat. Fat is present in peri-articular region near hip joint, and in the perineum, but is notably absent in the other subcutaneous areas. Medullary signal intensity is decreased in the visualized bones. **B. Similar image from a normal healthy female, showing subcutaneous and intermuscular fat, particularly in the gluteal region.** Fat is also noted in the retroperitoneal region, periarticular region near hip joint, in the perineum, and in the perirectal region.

Fig. 3 A. Axial MRI through feet in a patient with CGL showing prominent subcutaneous fat. Medullary signal intensity of the tarsals is decreased. B. Similar image from a normal volunteer showing presence of subcutaneous fat in the soles and in the bone marrow of the tarsals.

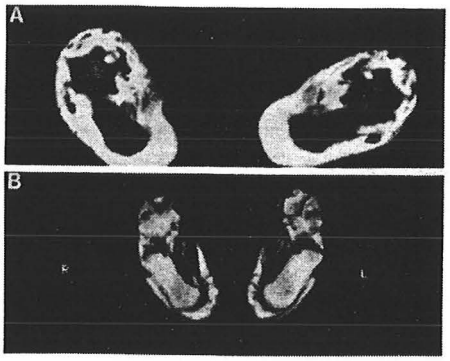


Table 3. Classification of Adipose Tissue

Metabolically-active	Mechanical
A. Subcutaneous sites -other than mechanical	A. Subcutaneous sites -scalp -temporal -buccal -palm -sole -vulvar
B. Intraabdominal -omental -mesenteric -retroperitoneal	
C. Intrathoracic -mediastinal -epicardial -retrosternal	B. Orbit
	C. Periarticular
	D. Epidural
	E. Crista galli
D. Bone marrow	F. Perineal
E. Parathyroids	G. Pericalyceal (kidneys)

The autopsy findings of our case confirmed previous clinical and autopsy reports of remarkable absence of subcutaneous adipose tissue in patients with CGL (17). Another site of "mechanical" adipose tissue, i.e., the pericalyceal region of kidney was revealed that was not evident on MRI. Virtual absence of intraparenchymal adipocytes from parathyroid glands was an interesting discovery. The rest of the parathyroid gland was normal histologically. Normal parathyroid glands contain ~ 15-50%. Therefore, absence of intraparenchymal adipocytes from parathyroid glands appears to be a feature of CGL and suggests that these adipocytes belong to the "metabolic" adipose tissue. Fat was also absent from the subcutaneous area overlying the breast tissue contrary to the observation in a previous autopsy report (18).

The liver is affected to varying degrees ranging from abnormal liver function tests and fatty liver to cirrhosis in all patients with CGL (1). In a previous report (18), 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. In other autopsies, marked hepatomegaly with severe fatty infiltration and fibrosis was noted in the 18-month-old boy and cirrhosis was seen in the 12½-year-old girl (19,20). Cirrhosis has also been reported in an 8-year-old girl with "total lipodystrophy", most likely CGL (21). At electron

microscopy, mitochondrial abnormalities such as swelling, irregular shapes, partial lysis of cristae, and flocculent matrix were noted in addition to an increase in the number of peroxisomes (21). The significance of these ultrastructural abnormalities, particularly as related to hypermetabolism in these patients, is not clear. Based on previous autopsies, it is widely believed that cirrhosis and its complications, i.e., hepatic failure, portal hypertension and variceal bleeding, are the leading causes of death in patients with CGL (8,11,18,22).

We also reported severe amyloidosis of pancreatic islets at autopsy (21). Intense staining of amyloid deposits was observed with immunostaining using anti-amylin antibodies. Amyloidosis involved 89% of the islets. However, islets, which were rich in pancreatic polypeptide-secreting cells, showed no amyloidosis. Immunostaining with anti-insulin and anti-glucagon antibodies revealed that the islets with amyloid deposits were markedly deficient in β cells but not in α cells. The ratio of β cells to α cells was reduced to 1:1, whereas the normal ratio is usually about 4:1.

Several investigators have observed echocardiographic features of hypertrophic cardiomyopathy in patients with CGL (25-27). Rheuban et al. (25) observed marked concentric left ventricular hypertrophy with a small left ventricular cavity in a 23-year-old female with CGL at autopsy. Myocardial cell hypertrophy was noted without any evidence of fatty infiltration or excessive glycogen storage. These investigators hypothesized that high plasma levels of insulin in CGL cause activation of IGF-I receptor resulting in myocardial hypertrophy (25). Enlargement of heart with hypertrophic subaortic stenosis and thickened interventricular septum were seen in one of the previous autopsies in a 29-year-old woman with CGL (18). On histology, diffuse interstitial fibrosis, irregular size and arrangement as well as hypertrophy of myocardial fibers in the interventricular septum and calcification of mitral annulus were observed (18). Hypertrophy of both left and right ventricular walls was also observed in an 18-month-old boy with CGL (19). In another autopsy case, however, the heart was reportedly normal (22). Our patient also did not have any evidence of myocardial hypertrophy either grossly or microscopically.

The presence of insulin-resistant diabetes mellitus and hypertriglyceridemia in patients with CGL may predispose them to premature atherosclerosis. Our patient had early atheromatous plaques in coronary arteries and fatty streaks in aorta. In previously reported autopsy reports, no aortic atherosclerosis was observed in a 20-year-old Japanese woman (22), but generalized atherosclerosis involving aorta, coronary arteries, and arteries of kidneys, pancreas and other organs has been reported in a 29-year-old Portuguese woman with CGL (18).

Patients with CGL may also be susceptible to other long-term complications of diabetes mellitus such as diabetic retinopathy, nephropathy and neuropathy. Both the nodular and the diffuse varieties of glomerulosclerosis have previously been reported in patients with CGL (18,27). Our patient also had diabetic arteriolonephrosclerosis and 3 months before her death; the daily urinary albumin excretion averaged 1.07 g (mean of three days collection). Another young patient of ours has developed nephrotic range proteinuria (5-8 g urinary albumin excretion per day) along with hypertension and severe proliferative diabetic retinopathy. Recently, she progressed to end-stage renal disease and requires hemodialysis. A kidney biopsy specimen showed severe diabetic glomerulosclerosis.

The other interesting finding at autopsy was normal sized ovaries but with thick fibrous cortices. Primary amenorrhea followed by irregular menstruation, hirsutism and clitoromegaly have been observed in some women with CGL. Some investigators have attributed these abnormalities to polycystic ovaries (28,29). In our patient, however, the gross anatomical features of polycystic changes, i.e., multiple large subcortical follicular cysts were not seen, although the cortical stroma appeared to be thick and fibrotic. Both the previous autopsies in adult women with CGL reported normal ovaries (18,22) and one of the patients had regular menstruation from age 18 until cessation at age 25 (18) and the other had irregular menstrual periods since menarche at age 15 (22). Therefore, presence of typical polycystic ovaries may not be a characteristic of patients with CGL.

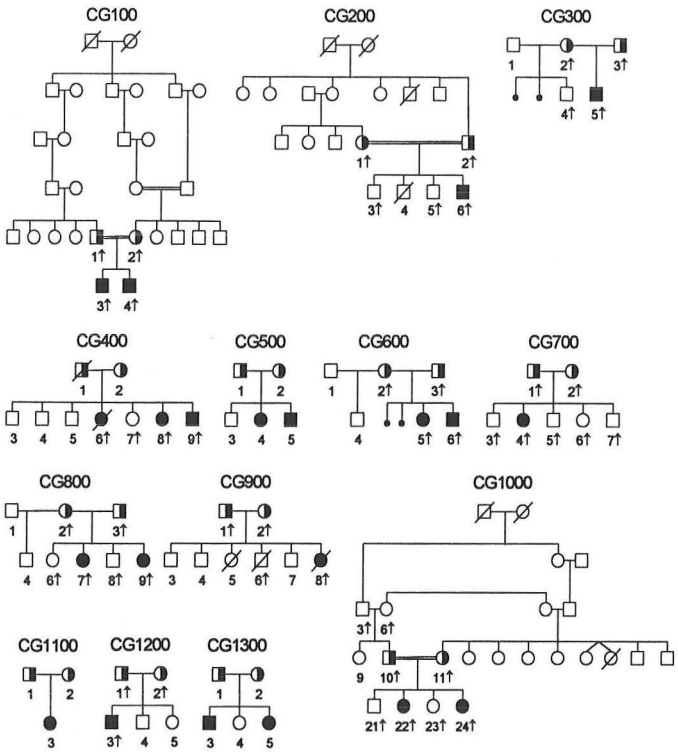
In the initial report by Seip (8), dilated ventricles and enlarged basal cistern were observed on a pneumoencephalogram in three patients with CGL. In another postmortem report on the 18-month-old boy with CGL, hamartomas of the hypothalamus were reported (19). However, no structural abnormality of the brain has been found consistently in patients with CGL on evaluation by computerized tomography (30). No brain pathology was found in our patient. Mid brain sections were normal in the autopsy report in the 20-year-old Japanese woman and in the 12½-year-old Polish girl (20,22). Four other patients examined by us with CGL also had normal MRI of the brain. These observations suggest that hypothalamic lesions are unlikely to be causally related.

Using radiographic skeletal surveys, MRI and technetium-99m bone scintigraphy, we have previously reported focal lytic lesions and some diffuse abnormalities limited to appendicular skeleton in three patients with CGL including the present case (14). The presence of lytic bone lesions in several other adult patients with CGL (12-15) suggests that these are not cystic angiomatosis, but are an inherent and unique feature of CGL. On bone biopsy, Guell-Gonzalez et al. (13) reported irregular and thin trabeculae and cystic areas with neovascularization from a cystic area. The presence of cystic areas rich in capillaries and thin walled veins in the section of humerus bone of our patient further confirms abnormal vascularity. The pathogenesis of these lesions, however, is not clear. One possibility is that patients with CGL are unable to replace their hemopoietic marrow tissue in appendicular skeleton with adipose tissue as is normally observed during childhood or adolescence, resulting in either persistence of cellular marrow or its partial replacement with vascular tissue. Thus, absence of marrow fat, persistence of hypercellular marrow and hypervascularity may all contribute to the development of lytic bone lesions in the appendicular skeleton after puberty in CGL.

On the basis of clinical features and the metabolic derangements in patients with CGL, the criteria for identification of CGL phenotype are given below:

Diagnostic criteria for CGL Phenotype

a. Generalized lack of body fat from birth **(essential criterion).**
b. Generalized extreme muscular appearance **(essential criterion).**
c. Acanthosis nigricans.
d. Acromegaloid features, i.e., enlarged hands, feet and mandible.
e. Umbilical hernia.
f. Clitoromegaly and mild hirsutism in women.
g. Severe fasting or postprandial hyperinsulinemia.
h. Onset of impaired glucose tolerance or diabetes mellitus during teenage.
i. Hypertriglyceridemia and low HDL cholesterol levels.
j. Characteristic distribution of body fat on MRI **(confirmatory).**



b. Genetic Studies

The genetic basis of CGL remains unknown. Several candidate genes, including the insulin receptor, beta-3 adrenergic receptor, apolipoproteins A2, C2, and C3, fatty acid binding protein 2, muscle glycogen synthase, insulin-like growth factor 1 receptor, insulin receptor substrate 1, hepatic lipase, hormone sensitive lipase, lipoprotein lipase, leptin and peroxisome proliferator-activated receptor γ (PPAR γ) have been excluded (31-35). We have assembled 13 CGL pedigrees (Fig. 4) and linkage studies are in progress.

Fig. 4 Congenital generalized lipodystrophy pedigrees. The pedigrees are numbered for identification. Each member of the family, whether alive or dead is assigned a number. Squares and circles indicate unaffected males and females, respectively; /, deceased subjects; half-filled symbols, obligate heterozygotes; filled symbols, affected status; •, a miscarriage; ↑, subject for whom DNA is available, diamonds with numbers written inside, other siblings, and double horizontal lines indicate consanguinity.

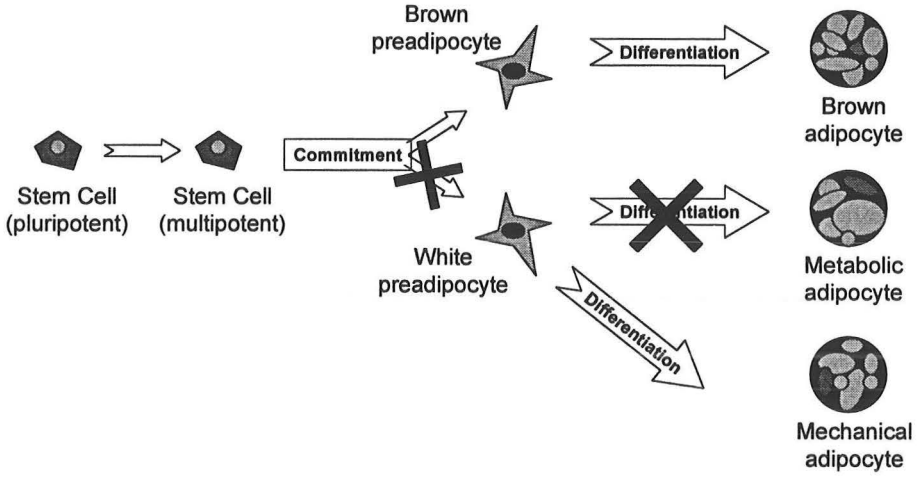


Fig. 5 Origin and differentiation of adipocytes and possible defects in CGL. Increasing commitment of pluripotent embryonic stem cells gives rise to multipotent stem cells of mesodermal origin from which adipocytes, muscle and cartilage originate. Multipotent stem cells committed to adipocyte lineage can form either brown or white preadipocytes which differentiate into brown or white adipocytes, respectively. We hypothesize that white preadipocytes differentiate either into metabolic or mechanical adipocytes. Differentiation of preadipocytes to adipocytes involves external inducers such as hormones and factors, second messenger pathways and transcription factors leading to induction of adipocyte-specific target genes. The possible defects in CGL are shown as crosses, i.e., agenesis of white preadipocytes, failure of preadipocytes to differentiate into mature metabolic adipocytes including the possibility of inability of mature adipocytes to synthesize and store triglycerides. Modified from Klaus (36).

The absence of fat could be the result of agenesis of preadipocytes, failure of preadipocytes to differentiate into mature adipocytes, or failure of mature adipocytes to synthesize and/or store triglycerides (Fig. 5). The genetic defect responsible for CGL may cause poor growth and development of "metabolic" adipose tissue but not that of "mechanical" adipose tissue (16). Therefore, transcription factors that are expressed during adipocyte differentiation such as CCAAT/enhancer binding proteins (C/EBP) α, β, δ, adipocyte determination and differentiation factor (ADD-1) or strerol responsive element-binding protein (SREBP1) and others adipocyte specific genes such as adipsin, GLUT4 etc. could be the candidate genes (Fig. 6; 36-38).

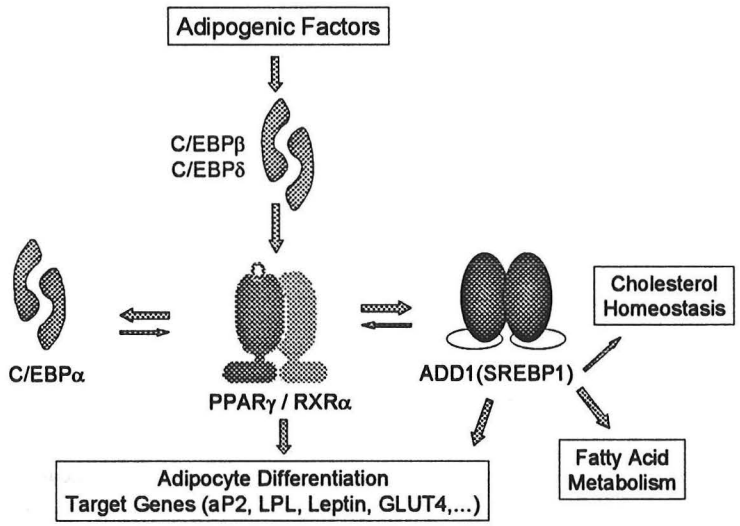


Fig. 6 Interaction between the key transcription factors that trigger adipocyte differentiation. Hormones induce a transient increase in the expression of C/EBP β and δ. These factors induce the expression of PPARγ, which provides the central trigger for the adipogenic program. ADD1 (SREBP1) is also induced early and in addition to regulating the genes important in fatty acid metabolism, increases the activity of PPARγ, possibly through generation of ligands. Terminal differentiation as well as maintenance of the fully differentiated state requires concerted action of PPARγ and C/EBPα. Modified from Brun et al. (37) and Schoonjan et al. (38).

Familial Partial Lipodystrophy, Dunnigan Variety (FPLD)

Ozer and co-workers (9) in 1973 described a 52-year old woman with a "new" variety of lipodystrophy. Several family members had a "fat neck" syndrome characterized by excessive accumulation of fat on the face, neck, shoulder girdle, axillae, back and genitalia. In contrast, the limbs were devoid of fat with prominent musculature and phlebectasia or severe varicosities. All nine affected subjects had hypertriglyceridemia, two had diabetes mellitus and four showed abnormal glucose tolerance. Subsequently, Dunnigan et al. (10) provided a more detailed description of two families with a similar type of lipodystrophy, which is now known as the familial partial lipodystrophy, Dunnigan variety (FPLD, OMIM # 308980).

Since these original descriptions (9,10), 13 other families with approximately 70 patients with FPLD have been reported (39-50). Assuming that only 25% of all such patients have been reported in the scientific literature, a conservative estimate of the prevalence of this disorder would be 1 in 25 million. Although initially thought to be due to an X-linked dominant inheritance (40), with the analysis of new pedigrees, the disease is now known to be transmitted as an autosomal dominant trait (47,50).

a. *Clinical features:*

With the onset of puberty, subcutaneous (sc) adipose tissue is lost from the extremities (arms and legs), giving rise to the characteristic "increased muscularity" in the arms and legs phenotype. A variable loss of fat occurs from the truncal area and subsequently excess fat may deposit in the head and neck areas. Infrequently, acanthosis nigricans, hirsutism, menstrual abnormalities and polycystic ovaries are observed. The affected males may have been previously under-reported because of difficulty in recognizing the "increased muscularity" phenotype. Furthermore, men with FPLD may not be as severely affected with metabolic complications of FPLD and insulin resistance as women with FPLD thus escaping attention of clinicians.

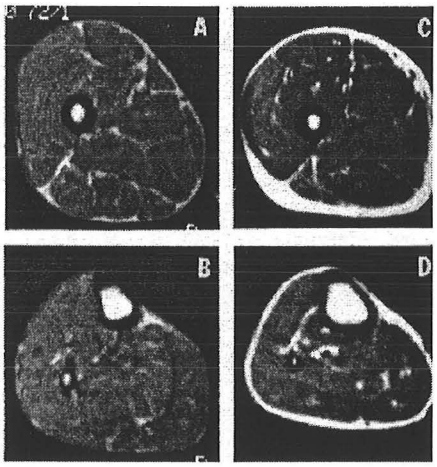


Fig. 7 Axial MRI at the level of thigh (A) and calf (B) in an affected woman with FPLD showing near complete absence of subcutaneous fat but preservation of intermuscular and bone marrow adipose tissue (increased signal intensity [brightness]). Scant sc adipose tissue can be seen in the medial and posterior aspects of the thigh. Similar images at the level of thigh (C) and calf (D) from a healthy female show normal amount of sc, intermuscular and bone marrow fat.

The MRI studies show a striking marked paucity of subcutaneous fat in both the lower and upper extremities in both sexes (Fig. 7). No differences in body fat distribution were detected between an affected male and three affected females (50). The absence of subcutaneous fat but preservation of fat in the intermuscular fasciae and femoral bone marrow is a diagnostic MRI feature in patients with FPLD (Fig. 7; 51). Further, as reported earlier by Robbins et al. (44) these patients have increased amount of intra-abdominal fat but reduced amounts of subcutaneous abdominal and truncal fat. The MRI studies also confirmed excessive fat in neck, face and submental areas. The diagnostic criteria for phenotype determination are given below:

Diagnostic criteria for FPLD Phenotype

a. Lack of subcutaneous fat from upper and lower extremities during childhood or puberty with normal physical appearance at birth **(essential criterion).**
b. Extreme muscularity in lower and upper extremities **(essential criterion).**
c. Excessive or normal adipose tissue in facial area and neck.
d. Acanthosis nigricans.
e. Mild to moderate fasting or postprandial hyperinsulinemia.
f. Onset of impaired glucose tolerance or diabetes mellitus after age 20.
g. Hypertriglyceridemia and low HDL cholesterol levels.
h. Characteristic distribution of body fat on MRI **(confirmatory)**.

The reported clinical and metabolic data in men affected with FPLD are scant. We have studied 39 patients with FPLD. Recognition of affected and unaffected females after the age of puberty can be made unequivocally (50). Precise characterization of affected and unaffected status is usually not possible in prepubertal children. Nonetheless, our preliminary data suggest that compared to women, men may be less prone to develop metabolic complications of insulin resistance. Women with FPLD had higher fasting plasma triglycerides concentrations ($P<0.01$) but lower high-density lipoprotein (HDL)

cholesterol concentrations (NS) compared to men with FPLD. In addition, the prevalence of overt diabetes mellitus in women and men with FPLD was 50% and 18%, respectively ($P<0.05$) compared to ~5 % in unaffected men and women.

There could be two mechanisms for these observations, (a) despite a similar pattern and extent of body fat distribution, men with FPLD may not be as insulin resistant as women with FPLD, and/or (b) if both the sexes have similar degree of insulin resistance, men may be relatively protected from the metabolic complications of insulin resistance. Our preliminary data show that fasting plasma insulin concentrations are not higher in women than men with FPLD. However, more data, particularly related to direct assessment of insulin sensitivity need to be collected to confirm our preliminary observations and to study pathophysiologic mechanisms of gender differences in metabolic complications caused by FPLD.

b. *Genetic Studies*

Using five well-characterized FPLD families, we have localized the gene for FPLD to chromosome 1q21-22 (50). The primary genetic defect could be related to the lack of expression of certain adipose tissue proteins/receptors, which induce growth, and maintenance of subcutaneous adipose tissue in the extremities, hip and truncal area in response to gonadal steroids at the time of puberty. Another possibility could be that the loss of adipose tissue at the time of puberty could be related to programmed cell death processes, i.e., cellular apoptosis. The accumulation of excessive adipose tissue in the head and neck areas as well as in the intra-abdominal region could possibly be a secondary phenomenon to compensate for the loss from the other areas.

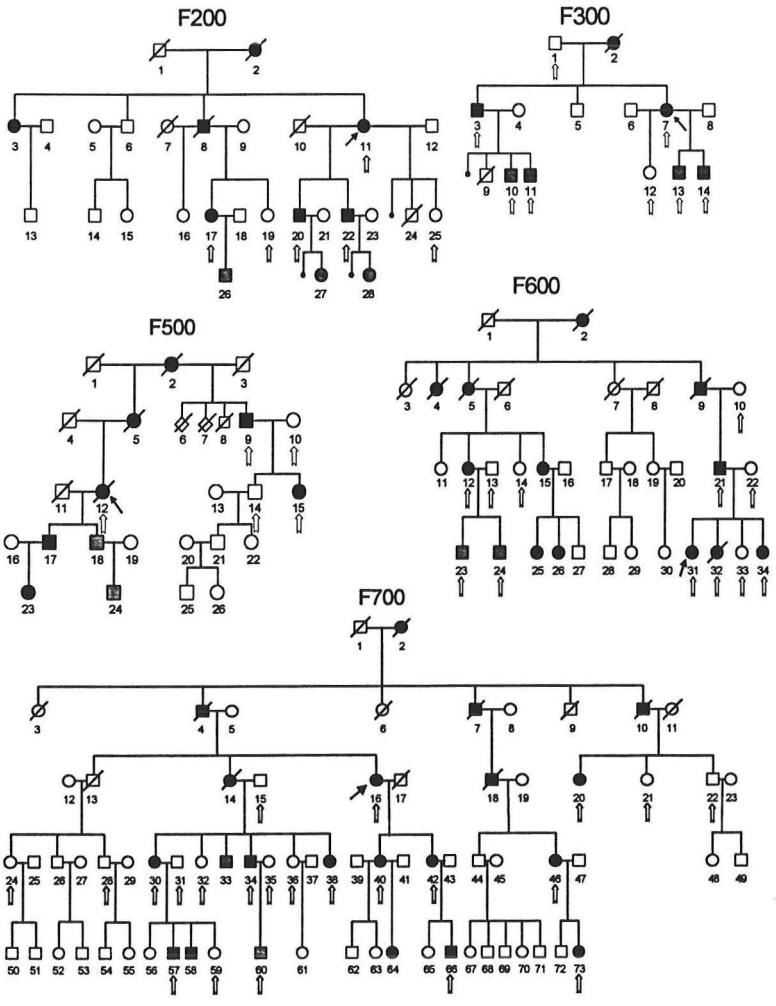


Fig. 8 Familial partial lipodystrophy pedigrees. The pedigrees and each member are numbered for identification. The phenotype in the deceased subjects was assigned on the basis of the clinical data, historical information and by viewing their pictures. Squares and circles indicate unaffected males and females, respectively; '/' indicates deceased subjects; filled symbols, affected status; gray symbols, phenotype uncertain (mostly children) and •, a miscarriage. The arrows indicate subjects for whom DNA is available.

We have assembled nineteen unique families with multiple affected subjects. Figure 8 shows the original pedigrees (50). We carried out genome–wide linkage scan with a set of highly polymorphic short tandem- repeats (STR) in 25 affected and 21 unaffected subjects from five well-characterized pedigrees (F200, F300, F500, F600 and F700 shown in Fig. 8) and mapped the FPLD locus to chromosome 1q21-22 (50). The maximum two-point lod score obtained with a highly polymorphic microsatellite at DIS2624 at θmax = 0 was 5.84.

Multipoint linkage analysis yielded a peak lod score of 8.25 between D1S305 and D1S1600 (Fig. 9). There was no evidence of genetic heterogeneity (α=1) in the pedigrees using the HOMOG program. Assuming reduced penetrance (80-90%) and a phenocopy rate of 1% made little difference to the maximum lod score or the placement of the FPLD locus (data not shown). Recently, Jackson et al. (51) have confirmed linkage to 1q21 in their FPLD families.

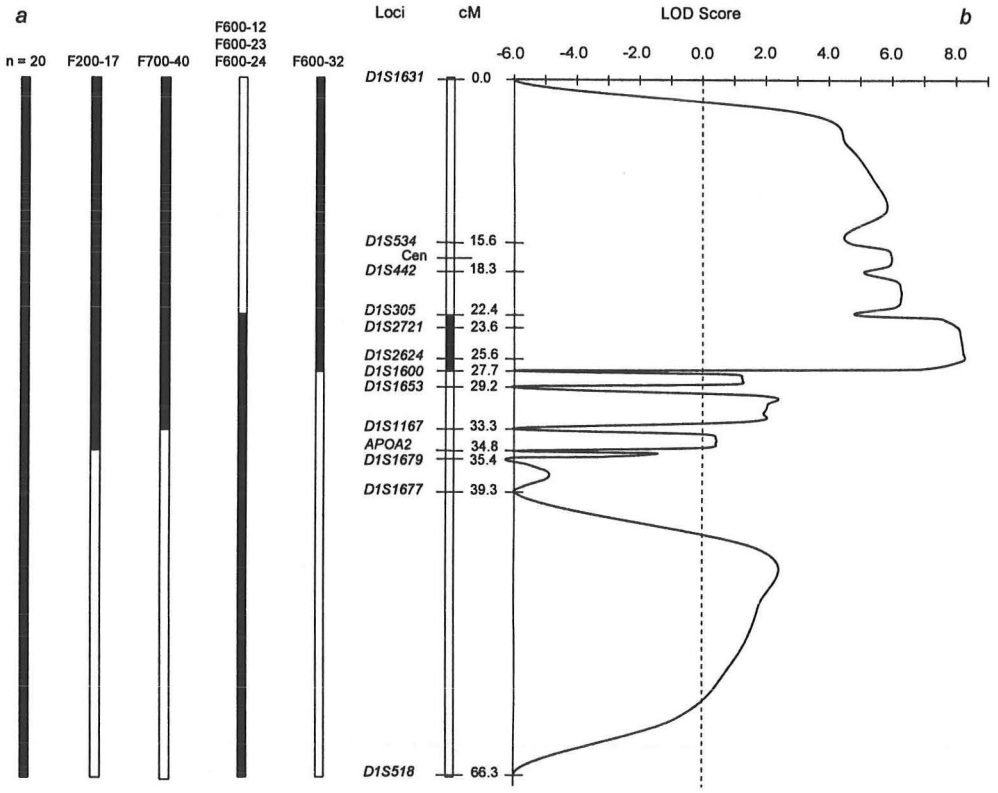


Fig. 9 Localization of the gene for FPLD (50). *a,* Filled portion of the vertical bar indicates the interval likely to harbor the *FPLD* gene based on haplotypes in the 24 affected individuals and two men who were initially classified as "uncertain" phenotype (F600.23 and F600.24) but share the same haplotype as their affected mother (F600.9) (The individuals are designated as shown in Fig. 7). Recombinants localize the defective gene to a 5.3 cM region between *D1S305* and *D1S1600* loci. The region of gene localization indicated by each recombinant is shown as the filled region of the locus bar. No adult, unaffected individuals possessed their families' disease haplotype in the critical region. The disease-associated haplotypes differed for each family. The location of the centromere is indicated by 'cen'; ApoA2 denotes a polymorphic microsatellite within an intron of the *apolipoprotein AII* gene. The extreme left bar denotes data from 20 affected subjects.

b, Multipoint analysis: The position of *D1S1631* was arbitrarily set at 0.0-cM and the positions of the other loci were fixed according to the sex-averaged distance determined with CEPH pedigree data. The total distance between *D1S1631* and *D1S518* is 66 cM. Multipoint lod scores on the x-axis are plotted against chromosome 1 loci on the y-axis.

We have searched several electronic databases for the known genes in the critical region including the Whitehead database, UNIGENE and Chromosome 1 specific sites. The critical region for *FPLD* gene contains several potential candidate genes such as cellular retinoic acid-binding protein type 2 (*CRABP2*) and aryl hydrocarbon receptor nuclear translocator (*ARNT*) (53,54). CRABP2 is a member of the intracellular lipid binding protein (iLBP) multigene family and is upregulated by retinoic acid. ARNT is considered to play a role in the regulation of xenobiotic metabolism as well as in growth, development and differentiation processes (55). Other known genes in the critical region are the high affinity receptor of immunoglobulin G, Fc gamma R1 (*FCGR1*), pyruvate kinase (*PKLR*) and histone H3 (*H3F2*). Genes encoding structural proteins of epidermal cornification and S100 calcium binding proteins map between *D1S305* and *D1S442,* and *apolipoprotein A2* gene maps between *D1S1600* and *D1S1677* and have thus been excluded. We have also initiated search for candidate genes in the region using physical mapping.

Familial Partial Lipodystrophies, Kobberling and other types

Kobberling et al. (39) reported another type of familial partial lipodystrophy in which the loss of adipose tissue in the Kobberling variety is said to be restricted to extremities only (39,40,42). Patients have normal amounts of fat in the face area and may have normal or even excess sc fat in the truncal area. The index case was a 24-year-old lady who had DM since age 11 and marked hyperlipidemia since age 16. The abnormal fat distribution was present since childhood. She had poor glycemic control with even 128 Units of insulin per day but was free from ketonuria. Examination revealed mild hepatomegaly and eruptive xanthomas. Both her 54-year-old mother and a 21-year-old sister were noted to have body habitus identical to her. Both of them had normal glucose tolerance but had mild hypertriglyceridemia. Kobberling et al. (39) also described two other sporadic cases with abnormal fat distribution as described in the previous family but no family members were available for examination. One of them was a 69-year-old woman with onset of DM at age 54 and the other was a 59-year-old patient with DM at age 52 and both had type IV hyperlipoproteinemia and mild hepatomegaly. In a subsequent paper, Kobberling et al. (42) reported another family in which a 64-year-old lady with DM since age 57 and severe hypertriglyceridemia and her daughter with normal oral glucose tolerance test and lipoproteins had marked paucity of fat in the extremities but well-developed fat in the face and trunk. The Kobberling variety has been reported in only two small pedigrees and four sporadic cases (39,40,42,56). The age of onset of lipodystrophy and the mode of inheritance are not clear.

In a review article, Kobberling and Dunnigan (40) hypothesized that both the types of FPL are due to X linked dominant inheritance and that the gene defect may be fatal in hemizygous state. Both the investigators described women with FPL and suggested that the disease does not affect men. In depth evaluation of metabolic and clinical features of affected patients from these families have not been undertaken.

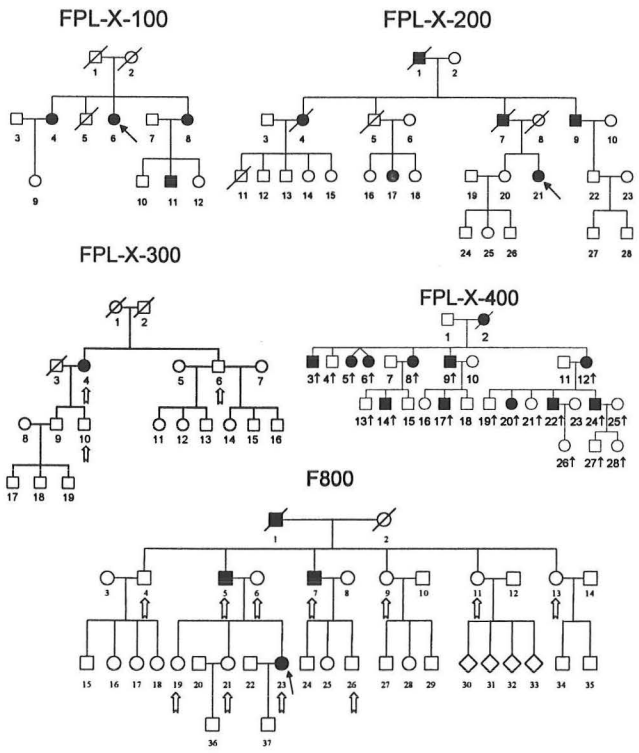


Fig. 9 Pedigrees with other types of familial lipodystrophies. Squares and circles indicate unaffected males and females, respectively; '/' indicates deceased subjects; and filled symbols, affected status. The arrows indicate subjects for whom DNA is available.

We have identified five families with familial partial lipodystrophy with distinct clinical features compared to FPLD patients (Fig. 9). Clinical features of FPLX100, FPLX200 and FPLX300 are consistent with the Kobberling variety of FPL. The affected patients have diabetes mellitus, hypertriglyceridemia and low levels of HDL cholesterol. Besides distinct clinical features, whole body MRI studies reveal marked differences in adipose tissue distribution between probands from these pedigrees and those with FPLD (unpublished data). The proband of the F800 pedigree had marked loss of sc fat from the extremities as well as from the face, palm and soles which is quite distinct from the fat loss observed in FPLD or CGL patients. Clinical features of affected subjects from the FPLX400 pedigree were recently described by Pardini et al. (57). The onset of lipodystrophy occurred after age 18. The patients have marked loss of sc fat from the face, neck, truncal area and extremities and showed acromegalic features (57). The clinical features therefore were clearly distinct from those of FPLD or CGL. Recent linkage studies showed that pedigrees F800 and FPLX400 do not map to chromosome 1q21.

ACQUIRED LIPODYSTROPHIES

Acquired Generalized Lipodystrophy (AGL)

AGL is a rare disease characterized by generalized disappearance of fat occurring after birth. AGL was originally described by Zeigler in 1928 (5). Of the seven patients with "lipodystrophy" described in that report, one patient, a 27-year-old female, had AGL (5). In that patient, tender swellings first appeared over the lower extremities at the age of 11 years, followed by rapid disappearance of subcutaneous fat in the same region. The disease was quiescent till 23 years of age, when during pregnancy, brown spots appeared on the skin followed by swelling over face and disappearance of all subcutaneous fat in the upper body and thus resulting in generalized lipodystrophy. She also had marked hepatosplenomegaly, high basal metabolic rate and diabetes mellitus.

In 1946, Lawrence (6) provided detailed description of clinical features and autopsy findings in a 26-year-old female with AGL. He also proposed five major criteria for the diagnosis of AGL, namely, (a). generalized absence of fat, (b). insulin resistant

diabetes mellitus, (c). absence of ketosis, (d). elevated basal metabolic rate and, (e). severe hyperlipidemia with hepatomegaly.

Since these two early reports, approximately 50 cases of AGL satisfying Lawrence's criteria have been published in the English literature (11,27,58-92). These criteria, however, fail to distinguish the acquired from congenital variety of generalized lipodystrophy (CGL) which was described later by Berardinelli and Seip (7,8). Therefore, it is difficult to ascertain in several cases whether the disease was acquired with onset during childhood or was CGL but not recognized at birth.

a. *Onset*

In most of the cases the disease begins in the childhood and adolescence. It is very rare for a patient to present after 30 years of age (86). In infancy, the recognition of this syndrome could be difficult since onset is often insidious over the period of months or years. Hence it is difficult to diagnose in early stages. However, a fully established case is easy to recognize due to characteristic loss of cheek fat pad, giving appearance of "early aging". The onset, however, can also be quite dramatic, and subcutaneous fat can disappear over a few weeks. Rarely, lipodystrophy can rapidly involve one part of body, remain quiescent over several months or years, and then in the same fashion, involve the rest of the body (5). This has been observed in one of the patients seen by us. Dramatic and rapid progression of lipodystrophy is often seen when it is preceded by a panniculitis like skin lesion (discussed later). Occasionally lipodystrophy is recognized after symptoms of marked hyperglycemia manifest.

b. *Preceding and Co-existing Events*

(i) Infectious Diseases: History of an infection may be obtained preceding the onset of AGL in a fair proportion of cases. These include varicella, measles, pertussis, diphtheria, pneumonia, osteomyelitis, parotitis, infectious mononucleosis, and hepatitis etc. Occasionally, evidence of several infections have been reported in a single patient (62,69). Although many of these early reports describe patients with antecedent infectious diseases; the temporal relationship between the onset of the infection and AGL is inadequate. Moreover, consistent association with any particular infectious agent is lacking. Thus although possible, a firm cause and effect relationship between a preceding infection and AGL is not established.

(ii) Panniculitis: Association between the painful tender subcutaneous swellings over various parts of the body suggestive of panniculitis and in some cases with a pathologically confirmed diagnosis of panniculitis and the initiation of AGL is rarely, though distinctly reported. A total of 10 such possible or definite cases have been described in the literature (5,6,76,79,78,83). The association and the onset was most dramatic in the case described by Zeigler (5). Other authors (78,79,83) have noted similar lesions over various parts of the body shortly preceding the diagnosis of AGL. Some of these cases, including three cases studied by us, show almost direct relationship between onset of nodular panniculitis and development of fat loss over the body. The interval between the onset of skin lesion to lipodystrophy is usually short but

variable. The lipodystrophy starts with the area of the skin lesion, and then rapidly spreads to the other parts of the body. Often, healing lesions of panniculitis leave behind depressed scars and hyperpigmentation (76,79). A pattern of spread, like annular expansion from a central lipoatrophic focus may also be observed (79). It is possible that the characterization of lipodystrophy differs when the same patient is seen at different stages of the disease. The same patient can be diagnosed as having localized lipodystrophy when seen early, and generalized disease when seen later.

Biopsy of such lesions reveals a lobular panniculitis with a mixed infiltrate of lymphocytes and mononuclear macrophages (78,79). In three such cases described by Billings (79), one developed generalized lipodystrophy, and the other two cases had almost total absence of subcutaneous adipose tissue with sparing of face. Another notable fact is that four out of six recently reported cases associated with panniculitis had either clinical or serological evidence of autoimmune diseases (Hashimoto's thyroiditis, juvenile rheumatoid arthritis, vitiligo, hemolytic anemia, chronic active hepatitis, and positive autoantibodies (ANF, Anti-Sm etc.) (78,79,83). It is not quite clear that the insulin dependent diabetes mellitus which preceded the onset of AGL in one of the patients was truly "autoimmune" as described by Billings et al. (79), or was a consequence of insulin resistance accompanying AGL syndrome. One of our patients also had progressive vitiligo at an early age, and later developed pernicious anemia. She also had positive serum anti-centromere antibody titers in the absence of clinical evidence of Calcinosis, Raynaud's Phenomenon, Esophageal Stricture, Sclerodactyly and Telengiectasia (CREST) syndrome. The clustering of a variety of autoimmune diseases in such patients is rather striking.

The course of the disease varies, but the data are limited for firm conclusions to be made. Usually the course is stationary once it becomes generalized, and ensuing morbidity and mortality is due to hyperglycemia and atherosclerosis. In some patients, however, there is a protracted course with appearance of new nodules and stepwise progression of AGL (79). Whether the course in such patients may be modified by the immunosuppressive therapy such as prednisolone, is questionable.

AGL associated with the lesions of panniculitis seems to be a distinct subentity of AGL. The clinical profile suggests possible autoimmune destruction of adipocytes, along with various other clinical or laboratory manifestations of autoimmune diseases. Detailed study of early histopathological lesions indicates that lymphocyte-mediated damage to adipocyte cell membrane may be an important process. Lipid is then lost in the interstitial space, followed by phagocytosis by mononuclear cells (79). This process explains localized necrosis of the fatty lobule and resultant atrophy. However, questions remain as to why lipodystrophy becomes generalized although initial lesions are those of localized panniculitis. Furthermore, if this disease is due to a generalized autoimmune phenomenon, why should it spare adipocytes at some selective places? All these questions remain to be answered.

(iii). Autoimmune Diseases: A total of 19 previously reported cases had some present or past evidence of connective tissue diseases. These included ten cases associated with panniculitis. Definite Sicca syndrome was present in two case (68,86), and there is suggestion of this syndrome at autopsy in the case described by Lawrence (6). Interestingly, vitiligo was present in three cases, including one of the cases seen by us

(71,83). Previous or present association with the other connective tissue diseases included; arthritis (86), dermatomyositis (86,91), thyroiditis, chronic active hepatitis (71,78), Hashimoto's thyroiditis, and juvenile rheumatoid arthritis (79). Positivity of autoantibodies without clinical evidence of connective tissue disease was also observed (78,79,87).

The clinical significance of association of autoimmune diseases without panniculitis with AGL is not quite clear at present. Whether the adipose tissue loss in these patients is also a part of a generalized autoimmune process cannot be entirely ruled out. Recently, Hubler et al. (91) reported autoantibodies against adipocyte membranes in a patient with AGL. Unlike the patients with panniculitis, however, there is no clinical evidence of immuno-inflammatory adipose tissue destruction preceding the onset of AGL. The course of the various autoimmune diseases in patients with AGL is also unknown.

(iv). Drugs: There are at least two reports of patients taking anti-epileptic medications, phenytoin and phenobarbital, preceding the onset of AGL (72).

c. *Sex Distribution*

There is a marked female preponderance of approximately 3:1.

d. *Physical Appearance*

Appearance in an established case is diagnostic. The face is devoid of fat, and cheeks are sunken. There may be a suggestion of exophthalmos (60). The subcutaneous fat is absent from abdomen, lower extremities and gluteal region. As a result of the disappearance of subcutaneous fat, underlying veins and muscles become prominent. Thyromegaly may sometimes be detected (62). Children, in particular, have marked abdominal prominence (27). This is more than that can be accounted for by hepatomegaly. Children often show increase in the linear growth as seen in the CGL, and may have acromegaloid features with large hands and feet (27,85).

Almost 1/3rd of the patients have acanthosis nigricans. It usually involves axilla, groin, neck, umbilicus, nipples and occasionally hands and feet. Mild hirsutism can be observed (27). Though there may be no sign of virilization, clitoral enlargement may be seen (27,76). Whether it is a true enlargement, or clitoris appears enlarged due to absence of fat is not clearly known. Abdominal ultrasound studies have demonstrated ovarian cysts in some cases (71,85,91).

Approximately 1/5th of the patients had eruptive xanthomas. In some cases, xanthomas disappeared with the treatment of hyperlipidemia. Hepatomegaly is a constant finding, occasionally, associated with cirrhosis. (58,59). Histology of the affected liver has revealed a variety of changes. These include; periportal round cell infiltration, fatty change, glycogen deposition, and fibrosis (27,74). Fatty deposition in the liver may be due to diabetes mellitus and hypertriglyceridemia. However, the pathogenesis of cirrhosis in acquired lipodystrophy is not clear at present. Splenomegaly has been observed (5,6,58,62,65,73,76,83). Lymphadenopathy associated with acquired lipodystrophy has been seen in association with Sicca Syndrome (68), and without any obvious cause (80).

Acquired Partial Lipodystrophy (APL)

APL is also known as the Barraquer-Simons syndrome, progressive lipodystrophy or cephalothoracic lipodystrophy (3,4). An episode of acute viral illness precedes the onset of fat loss, which occurs initially from the facial area and then spreads to involve neck, shoulders, upper extremities (both arms and forearms), thoracic region and upper abdomen. In an occasional patient, fat loss may extend up to the inguinal region or thighs. Although many patients describe fat loss over a period of 18 months, occasionally fat loss may occur at periodic intervals over a total duration of several years (~6 y). In most of the cases, fat in the hips and lower extremities (legs) remains unaffected and can accumulate in excess in women after puberty.

A recent review of a total of 140 patients including 14 patients evaluated by us reveals a female preponderance (female to male ratio 2.6:1) (92-151). In >90% of the patients, the onset was before the age of 16 years; the median age of onset of APL being 8 years. Patients with APL generally do not have metabolic abnormalities associated with insulin resistance such as hypertriglyceridemia and diabetes. Diabetes was reported in 5 patients but was most likely due to secondary causes.

The most frequent associations of APL are with glomerulonephritis (GN), hypocomplementemia, and presence of C3 nephritic factor (C3NeF) in the serum. Senior and Gellis (27) reported association of APL with GN, predominantly membranoproliferative variety (MPGN), which is also known as mesangiocapillary GN (MCGN) or dense deposit disease. Approximately, one-third of the patients develop MCGN or other forms of GN. Onset of APL usually precedes the onset of GN. The median age of onset of GN and APL in our review was 19 and 6 years, respectively. Serum C3 levels were universally low except in a few patients. Levels of C1q, C4, C5, C6, and Factors B and P (properdin) have been reported to be normal in most of the patients (109). In 1969, Spitzer et al. (152) found that sera from patients with MCGN split the C3 in the normal serum and thus the name C3 nephritic factor (C3NeF). C3 NeF is an immunoglobulin mostly of the IgG class (153,154). Up to 90% of the patients with APL have serum C3NeF. The possible mechanisms by which C3NeF activates alternative complement pathway are shown in Fig. 10.

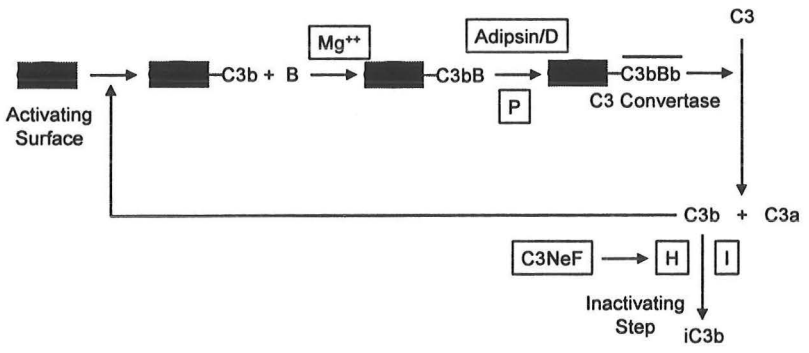


Fig. 10 Activation of the alternative complement pathway. C3b the major active fragment of C3 cleavage is attached to the activating surface through an ester or an amide bond. B,D,P,H and I indicate factors B, D, properdin, H and I, respectively. C3bBb (C3 convertase) splits C3 into C3b and C3a. The complex C3bBbC3b further activates C5-9 causing lysis of cells (not shown). C3NeF indicates C3 nephritic factor. Amplification occurs by the positive feedback loop that is held in check by Factors H and I, both of which inactivate C3b to iC3b. C3NeF binds to factor H and thus interferes with inactivation of C3b, thus permits amplification of the alternative pathway through positive feedback loop.

APL may be associated with other autoimmune diseases. Systemic lupus erythematosus (SLE) has been reported in 6 patients (117,138,143,145), dermatomyositis (136), hypothyroidism and pernicious anemia (151), celiac disease (136), dermatitis herpetiformis (136), rheumatoid arthritis (117) and temporal arteritis in 1 patient each (117), and leukocytoclastic vasculitis in 2 patients (27,131). SLE was diagnosed 2-28 years after the onset of APL. Several patients with APL may also have antinuclear (ANA) and anti double-stranded DNA (Anti-dsDNA) antibodies.

The exact pathogenesis of APL and associated MCGN is not clear. Recently, glomerulonephritis has been reported in humans and Yorkshire pigs with factor H deficiency suggesting a critical role of factor H in interfering with the positive feedback loop in the alternative complement pathway (155-158). It is proposed that binding of C3NeF to factor H interferes with factor H activity and thus creates a state similar to factor H deficiency. Although this mechanism may be relevant to the pathogenesis of MCGN in patients with C3NeF, it may not be related to the causation of APL.

The lysis of adipocytes in APL may in fact be related to the expression of several complement proteins such as factors D (adipsin), B, P (properdin), H and complement C3 (159-161). C3a desarg is also known as acylation stimulating protein (ASP). Recent data suggest some heterogeneity in the expression of factor D in adipose tissue from different anatomical location (162). There is a possibility that APL may be caused by C3NeF mediated lysis of adipose tissue expressing factor D (Fig. 11) (159). However, this remains to be confirmed.

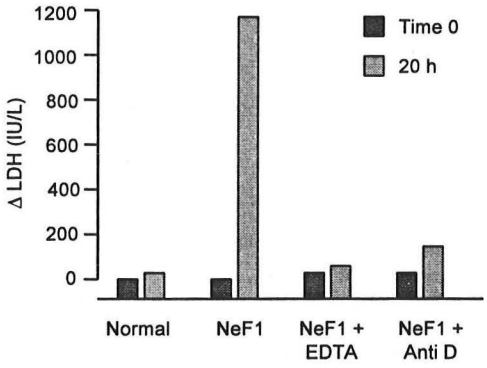


Fig. 11 Change in LDH activity from baseline in infranatants from incubation of adipocytes from rat epidydmal fat pad with normal and nephritic factor (NeF) containing serum. Adipocyte lysis was abolished in the presence of EDTA, which chelated divalent cations and prevents complement activation and was reduced by an antibody to Factor D. From Mathieson et al. (159).

Localized lipodystrophies

Localized lipodystrophies are defined as a localized loss of sc adipose tissue from small areas or from parts of a limb. It is characterized by single or multiple, well-demarcated areas showing atrophy of sc adipose tissue. Clinical features reveal depressed areas corresponding to the loss of sc fat. In some patients, panniculitis, i.e., lymphocytic infiltration of the adipose tissue is noted in the perivascular areas. In others, there are no signs of inflammation at the site of lesion. The classification of localized lipodystrophies is given below.

Various types of localized lipodystrophies

1. Drug injections such as insulin, steroids, antibiotics etc.
2. Pressure-induced semicircular lipoatrophy of the thighs.
3. Weber-Christian syndrome, connective tissue panniculitis, lupus panniculitis.
4. Centrifugal lipodystrophy.

5. Idiopathic.

1. *Drug-induced localized lipodystrophy*

Localized lipodystrophy was a frequent complication of insulin therapy prior to the availability of purified insulin or human insulin. Although impurities in insulin preparation were considered to be causing lipoatrophy, other mechanisms such as presence of lipases, repeated trauma or an autoimmune process could also be involved (163,164). The presence of high-titers of anti-insulin antibodies, deposition of IgA and C3 locally and response to local corticosteroid therapy strongly suggest an autoimmune phenomenon. A recent report suggests that in some cases lipodystrophy may be due to local high production of tumor-necrosis factor (TNF) -α leading to dedifferentiation of sc adipocytes. Other drugs such as steroids and antibiotics have also been reported to cause localized lipodystrophy (165-167).

2. *Pressure-induced localized lipoatrophy*

Repeated pressure against any region can result in atrophy of the sc adipose tissue resulting in localized lipodystrophy (168). In a few patients, repeated pressure against anterior aspect of the thigh due to pressing it against the washbowl when applying make up has been reported to cause a localized semicircular lipoatrophy. Recurrent microtrauma or reduced perfusion may cause atrophy of the adipose tissue. Avoidance of pressure may result in partial improvement.

3. *Panniculitis and localized lipodystrophy*

As described earlier, some patients with acquired generalized lipodystrophy have acute panniculitis or Weber-Christian syndrome characterized by perivascular infiltration of lymphocytes in the adipose tissue. In some patients, progression to generalized lipodystrophy does not occur. Instead, patients may have several areas of localized lipodystrophy (169). Anatomic distribution of lipodystrophic lesions closely follows the area of inflammation and does not spread beyond it. If the process causes only localized or partial lipodystrophy, insulin resistance and its metabolic consequences may not be present. Lymphocytic infiltrate can be documented at the beginning of the evolution of lipodystrophy but not long after the lesions have been there. Many patients may have positive titers of serum ANAs or anti dsDNA antibodies. Some patients may have clinical manifestations of systemic lupus erythematosus (SLE) or other autoimmune diseases (170-172). Whether the lesions respond to corticosteroid therapy, local or systemic, is not clear.

4. *Centrifugal lipodystrophy*

In 1971, Imamura and co-workers reported a peculiar type of lipodystrophy in 5 patients and termed it as "Lipodystrophia centrifugalis abdominalis infantilis" (173). It was characterized by a depression of the skin resulting from the loss of sc fat from the abdomen and adjacent regions, centrifugal spread, and slightly erythematous and scaly changes in the surrounding areas and onset before the age of 3 years. The skin in other

areas and other organs were not involved. Histopathology reveals loss of sc fat and inflammatory cells such as lymphocytes and histiocytes in the surrounding areas. Approximately half of the patients may have regional lymphadenopathy. More than 100 patients have been reported from Japan, Korea and Singapore (174,175). Only a few reported patients are Caucasian and it is doubted whether they have classical centrifugal lipodystrophy. The exact etiology remains unknown. The centrifugal spread of the lesions ceases in 3 years in ~50% of the patients and in 8 years in more than 90% of the patients. After cessation of the spread of lesions, more than 50% of the patients show complete or partial improvement spontaneously. Corticosteroids do not stop the enlargement of the depressed lesions.

5. *Idiopathic lipodystrophy*

In some patients with localized lipodystrophy, known etiologic factors mentioned above are not evident and thus those can be classified as having idiopathic lipodystrophy (167,176,177).

Human immunodeficiency virus (HIV)-1 protease inhibitors-induced lipodystrophy

HIV-1 protease plays a key role in viral maturation (Fig. 12). Inhibition of HIV-1 protease results in non-infectious particles. The combination therapy that includes HIV-1 protease inhibitors has dramatically improved the long-term survival of patients infected with HIV-1. However, recently several reports indicate development of lipodystrophy in HIV patients on long term therapy with the protease-inhibitors (178-181).

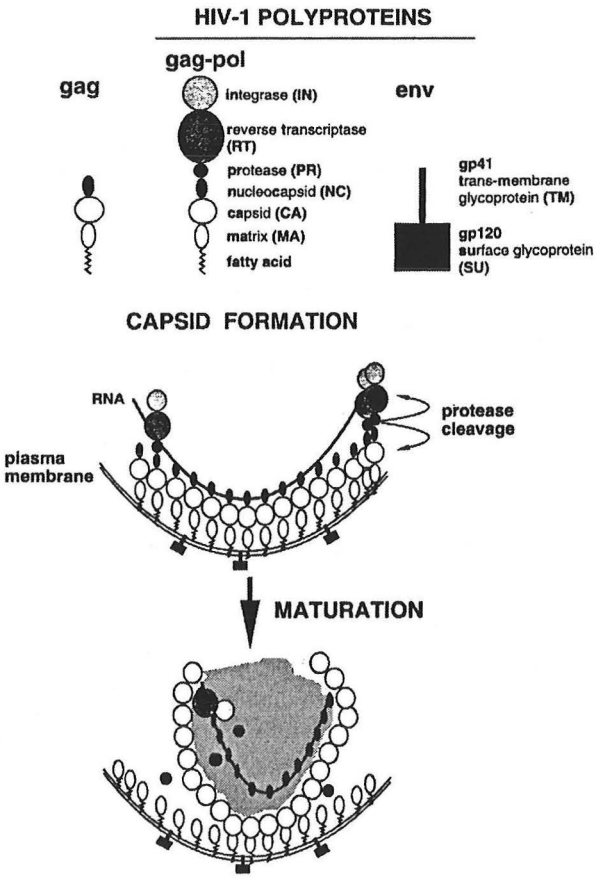


Fig. 12 HIV-1 capsid assembly and maturation. The involved proteins gag, gag-pol and env are schematically depicted. HIV-1 protease is an aspartic protease and its appropriate activation is essential for viral maturation. From Pavlakis GV (182).

The protease inhibitors-induced lipodystrophy is clinically characterized by marked reduction in sc fat from the face and both the upper and lower extremities including the gluteal region. Affected subjects develop increased muscularity in the arms and legs with prominent superficial veins. At the same time excess fat accumulates in

the neck and truncal region causing "double chin", "buffalo or camel hump", and "crix-belly (related to Crixivan or Indinavir therapy)". These patients are more likely to develop features of insulin resistance such as impaired glucose tolerance or diabetes mellitus and hypertriglyceridemia. Pronounced changes in fat distribution usually occur after receiving protease inhibitors for more than 1.5-2.0 years, whereas changes in glucose and lipid metabolism may be noticeable much earlier.

The precise mechanisms by which the protease inhibitors induce such changes in fat distribution, cause insulin resistance and other metabolic aberrations are not understood. Because of some similarities in fat distribution in these patients and those with Cushing's syndrome, hypercortisolemia has been excluded (178). Recently, Carr et al. (183) have hypothesized that these changes are related to > 60% homology between the 12 amino acid polypeptide catalytic region of HIV-1 protease and CRABP-1 and the lipid binding domain of the low-density receptor-related protein (LRP). They hypothesize that the protease inhibitors can cause functional inhibition of CRABP-1 and LRP which are involved in adipocyte differentiation and lipid metabolism, respectively thus causing both abnormal fat distribution pattern and hypertriglyceridemia. This hypothesis although attractive remains to be proven.

DIFFERENTIAL DIAGONSIS OF LIPODYSTROPHIES

SHORT Syndrome

The SHORT syndrome with the clinical manifestations of ***s***hort stature, ***h***yperextensibility of joints and/or inguinal hernia, ***o***cular depression, ***R***eiger anomaly and ***t***eething delay was described by Gorlin et al. (184) and Sensenbrenner et al. (185). Reiger anomaly constitutes eye abnormalities such as hypoplasia of iris stroma, prominent Schwalbe ring, iridocorneal synechiae, micro or megalo cornea, strabismus, and predisposition to glaucoma; and tooth abnormalities such as hypodontia, microdontia, enamel hypoplasia and atypically shaped and positioned teeth. Other clinical features may include slow weight gain, distinct facial abnormalities like disproportionately small face, sunken eyes and wide nasal bridge with prominent pinnae, inguinal hernia, systolic ejection murmur and partial lipodystrophy. Infrequently, patients may have bilateral symmetrical lens opacities (186), deafness (187) and insulin resistant diabetes mellitus (188). To date, only 10 patients with SHORT syndrome have been reported in the literature (184-191). Inheritance appears to be autosomal recessive although Aarskog and co-workers (192) described a similar syndrome but dominantly inherited disorder affecting four individuals in three generations.

Most of the patients have lipodystrophy involving primarily the face (8/10), upper extremities (6/10), chest (4/10) and abdomen (1/10). Lower extremities and gluteal region is usually spared. The patient described by Aarskog et al. (192), however, had localized loss of subcutaneous fat from the gluteal region, in addition to the loss of facial fat. Systematic evaluation of the loss of fat in these patients using anthropometry or imaging techniques has not been undertaken.

Mandibuloacral Dysplasia

Mandibuloacral dysplasia is an autosomal recessive condition first described by Young et al. (193) and Sensenbrenner et al. (194). The clinical features include short stature, high pitched voice, craniofacial anomalies like Wormian bones of the skull, beaked nose, facial hypoplasia, premature loss of teeth, and progressive mandibular hypoplasia; skeletal anomalies including clavicular and rib hypoplasia, acroosteolysis and stiff joints; and ectodermal defects like skin atrophy, alopecia and nail dysplasia (193-204). The patients have a normal mental development and life span. Insulin resistance and diabetes mellitus was reported in one patient and lipodystrophy was noted in two patients (195,196). In one patient, lipodystrophy was characterized by loss of sc fat in the extremities and in the trunk below the level of the nipples, whereas in the other, sparing of the neck and face was noted (196). Other investigators, however, have reported atrophy and thinning of the skin over the extremities only without reference to the loss of sc fat. Thus, whether lipodystrophy is a consistent feature of patients with mandibuloacral dysplasia and if so, whether there is a peculiar pattern of lipodystrophy are not clear.

Werner's syndrome (Progeria)

Werner's syndrome is an autosomal recessive disorder with clinical features of short stature, bird like appearance with beaked shape nose, premature loss and greying of hair, scleroderma-like skin changes and skin ulceration (205). Osteoporosis and profound wasting of the limb musculature is characteristic. Because of marked thinning of the arms and legs, these patients may be misdiagnosed as having lipodystrophy, however, sc fat is well preserved.

Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome)

This syndrome was first described by Rautenstrauch and co-workers in 1977 (206) in two sisters with congenital malformations reminiscent of progeria. In 1979, Wiedemann defined a new progeroid syndrome based on his two personal observations and the earlier report (207). To date, nine other cases with this rare syndrome have been reported (208-210).

The syndrome is characterized by a progeroid face (triangular, old-looking face with relatively large skull, prominent veins especially of the scalp, sparse scalp hair, large anterior fontanelle) and nearly total absence of sc fat (giving the clinical appearance of prominent veins and muscles). SC fat, however, is evident in the gluteal area. These features are apparent at birth and therefore this syndrome needs to be differentiated from congenital generalized lipodystrophy. Inheritance seems to be autosomal recessive.

Severe weight loss (malnutrition, famine, anorexia nervosa, malabsorption syndromes, cachexia, thyrotoxicosis, adrenocortical insufficiency)

Severe weight loss and resultant lack of adipose tissue can be mistaken for acquired or congenital generalized lipodystrophy. However, patients with severe weight

loss have lack of adipose tissue as well as atrophy of skeletal muscles. Presence of other clinical features should make it easy to differentiate these disorders from lipodystrophies.

Multiple symmetric lipomatosis

Multiple symmetric lipomatosis (MSL, Madelung's disease, Launois-Bensaude syndrome or benign symmetric lipomatosis) is a rare disorder of adipose tissue which usually affects adult males (male to female ratio ranging from 4:1 to 15:1) (211-214). Most of the patients have a preceding history of heavy alcohol intake. It is characterized by a progressive growth of nonencapsulated subcutaneous (sc) adipose tissue symmetrically localized in the cervical, shoulder, chest, back, abdominal and groin regions (211,214). SC adipose tissue in the distal parts of upper and lower extremities, however, may be reduced. Symmetric lipomatous involvement in the deep cervical region and mediastinum has been observed in some cases. History of alcohol abuse is strongly associated with MSL, and therefore a causal role of alcohol in the pathogenesis in MSL is postulated. Cessation of alcohol intake is advisable, but the fat masses may not decrease in size or may even progress for several years afterwards. The underlying factors that predispose subjects with heavy alcohol consumption to develop MSL remain unknown.

Cushing's syndrome

Many patients with FPL, Dunnigan variety have a cushingoid appearance and should be differentiated from those with Cushing's syndrome. Absence of buffalo hump, abdominal striae and facial erythema are useful differentiating features clinically. Laboratory studies in FPLD patients do not show evidence of hypercortisolemia.

MANAGEMENT

Cosmetic management of patients with lipodystrophy constitutes of facial reconstruction with free TRAM flaps, transposition of facial muscle and silicone or other implants in the cheeks. In patients with acquired partial lipodystrophy, adipose tissue transplantation from abdomen or lower extremity to facial area has been tried with variable results. In some patients transplanted fat atrophied whereas in others it lasted for several years. Women with acquired partial lipodystrophy who have cosmetic problems due to marked excess of fat in the hips and legs should be advised to lose weight to improve their physical appearance. Several patients with FPL, Dunnigan variety have undergone liposuction or lipectomy for removal of excess facial fat or fat in the neck area. Weight loss in these patients can also result in reduction of facial and neck fat and disappearance of double-chin.

Another cosmetic problem particularly in patients with CGL pertains to severe acanthosis nigricans. There is no specific therapy available for reducing the pigmentation or hypertrophy of the skin. Anecdotally, etretinate and fish oil therapy have improved acanthosis in patients with generalized lipodystrophy (215,216).

The optimum dietary therapy for these patients is not clear for lack of clinical trials. In general, because of extreme hypertriglyceridemia and chylomicronemia in

patients with CGL, AGL and FPLD, a low-fat diet is recommended. However, low-fat, high-carbohydrate diets can also induce hypertriglyceridemia and lower HDL cholesterol levels. It seems that patients with FPL should avoid weight gain to reduce the risk of developing diabetes and dyslipidemia. However, whether long-term reduction in energy intake is beneficial in patients with CGL or AGL, is not clear. Children with CGL or AGL certainly should consume enough energy to allow for growth and maturation.

There are no clinical trial data available about the efficacy of various hypoglycemic drugs, such as, insulin, oral sulfonylureas, metformin and troglitazone. In my experience, many patients with CGL require extremely high doses of insulin (some may require U-500 insulin) to control hyperglycemia. Insulin requirements of patients with AGL or FPL may also be high due to insulin resistance. Good glycemic control should benefit these patients in preventing complications of diabetes such as nephropathy, retinopathy, neuropathy and possibly, atherosclerosis.

The efficacy of various lipid-lowering drugs, particularly, fibrates, fish oil and statins has not been studied. Severely hypertriglyceridemic patients should be treated with fibrates and/or fish oil (n-3 polyunsaturated fatty acids). Occasional patient may require combination therapy with fibrates and statins. Rigorous control of diabetes remains the most efficacious way to lower serum triglyceride concentrations and should be emphasized. Women should avoid use of estrogens for oral contraception or for postmenopausal hormone replacement therapy as it may accentuate hypertriglyceridemia.

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