

Lipedema: An Inherited Condition

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Received 28 April 2009; Accepted 12 December 2009

Lipedema is a condition characterized by swelling and enlargement of the lower limbs due to abnormal deposition of subcutaneous fat. Lipedema is an under-recognized condition, often misdiagnosed as lymphedema or dismissed as simple obesity. We present a series of pedigrees and propose that lipedema is a genetic condition with either X-linked dominant inheritance or more likely, autosomal dominant inheritance with sex limitation. Lipedema appears to be a condition almost exclusively affecting females, presumably estrogen-requiring as it usually manifests at puberty. Lipedema is an entity distinct from obesity, but may be wrongly diagnosed as primary obesity, due to clinical overlap. The phenotype suggests a condition distinct from obesity and associated with pain, tenderness, and easy bruising in affected areas. © 2010 Wiley-Liss, Inc.

Key words: lipedema; lymphedema; lipodystrophy; autosomal dominant; X-linked dominant

INTRODUCTION

Lipedema is a disorder of adipose tissue that occurs almost exclusively in women. It was first described by Allen and Hines [1940] as bilateral enlargement of the legs thought to be due to abnormal deposition of subcutaneous fat and accumulation of fluid in the lower legs. Affected individuals develop bilateral and symmetrical "fatty" non-pitting swelling usually confined to the legs and hips [Wold et al., 1951]. The feet are typically spared, giving rise to an "inverse shouldering" effect at the ankles. Patients may complain of tenderness and easy bruising of the affected areas. Disease onset is usually at or soon after puberty but can develop at other times of hormonal change such as pregnancy or even menopause.

Wold et al. [1949] proposed a set of diagnostic criteria for lipedema almost a decade after Allen and Hines' [1940] paper. These criteria are still in use today:

- (i) occurrence almost exclusively in women;
- (ii) a bilateral and symmetrical nature with minimal involvement of the feet, resulting in an "inverse shouldering" or "bracelet" effect at the ankle;

How to Cite this Article:

Child AH, Gordon KD, Sharpe P, Brice G, Ostergaard P, Jeffery S, Mortimer PS. 2010. Lipedema: An inherited condition. *Am J Med Genet Part A* 152A:970–976.

- (iii) minimal pitting edema;
- (iv) pain, tenderness, and easy bruising; and
- (v) persistent enlargement despite elevation of the extremities or weight loss.

Lipedema is thought to be uncommon but no prevalence data exist within the medical literature. Based upon our own regional Dermatology Department, a minimum estimate of prevalence within the population would be 1 in 72,000. This is likely to be a significant underestimate due to problems with misdiagnosis or failure of referral by community physicians. We have ascertained 67 cases within the last 15 years via our lymphedema/lipedema clinic.

The diagnosis of lipedema is not always simple to differentiate from obesity. The prevalence of obesity may be assessed by using body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). A BMI over $25 \text{ kg}/\text{m}^2$ is defined as overweight, and a BMI of over $30 \text{ kg}/\text{m}^2$ as obese [WHO "Obesity and Overweight," 2010a]. Patients with lipedema may also have elevated BMIs but whilst obesity will respond to restricted dietary intake, lipedema will not, leading to a wasted

Grant sponsor: Bluff-Field Charitable Fund, St. George's, University of London; Grant sponsor: St. George's NHS Hospital Trust; Grant sponsor: Daphne Jackson Trust; Grant sponsor: British Skin Foundation.

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Published online 23 March 2010 in Wiley InterScience
(www.interscience.wiley.com)
DOI 10.1002/ajmg.a.33313

upper body and a lower body that stubbornly remains the same shape from the waist to the ankles. In a teenager or young adult, a pure lipedema is characteristic for the following reasons: disproportionate distribution of fat below the waist, and the coexisting features such as tissue tenderness and easy bruising. The lack of response to weight-reducing diets would argue against a form of obesity. However, later in life lipedema can be complicated by obesity or lymphedema, in which case, historical symptoms are key to the diagnosis.

Lipedema must be differentiated from lymphedema, another cause of bilateral lower limb enlargement. Primary lymphedema may arise from an intrinsic abnormality of lymph drainage, for example, genetically determined hypoplasia or dysfunction of lymphatic vessels [Mortimer, 2004]. Secondary lymphedema may result from lymphatic damage due to an extrinsic cause, for example, surgical lymphadenectomy. Lymphedema typically results in asymmetrical edematous swelling due to excess accumulation of interstitial fluid within tissue spaces due to inadequate lymph drainage of protein, cells, and fluid. Typical features of lymphedema include brawny, hard, and warty changes of the skin and subcutis. Kaposi–Stemmer sign is pathognomonic of lymphedema [Stemmer, 1976], and represents the inability to pinch or pick up a fold of skin at the base of the second toe because of its thickness. Pitting (skin remains indented for a few minutes after removal of firm finger pressure for 30 sec) is often present during the initial stages but may become less apparent over time. In contrast, skin changes and pitting are almost always absent in lipedema. Other points of clinical differentiation between the two conditions are found in Table I. A recent review of clinical aspects of both lipedema and lymphedema is given by Kroger [2008].

A number of investigations have been undertaken in patients with lipedema, including histological studies [Stallworth et al., 1974], lymphoscintigrams, venograms, arteriograms, and magnetic resonance lymphangiography, all failing to demonstrate specific abnormalities, but suggesting a subclinical reduction in lymphatic function [Beninson and Edelglass, 1984; Amman-Vesti et al., 2001; Boursier et al., 2004; Lohrmann et al., 2009]. Lipedema can be complicated by secondary lymphedema, resulting in the clinical picture of lipo-lymphedema. Allen and Hines [1940] proposed that the progressive edema formation in lipedema was the result of poor resistance of accumulated fat against the hydrostatic passage of fluid from the capillaries into the interstitium. Surgical experience has indicated increased fat deposition around the inguinal lymph nodes presumably causing nodal and lymphatic compression, leading to secondary lymphedema.

We are now closer to understanding the pathogenesis for the abnormal deposition of fat in patients with lipedema. A greater understanding of these mechanisms through medical research may lead to the development of therapeutic interventions in the future.

Frequent observations of mother-to-daughter mode of inheritance led us to hypothesize that lipedema is a genetic disorder. The main aim of the study was to find evidence to support an inherited basis for the disorder. We proceeded to explore the family history of all known patients with lipedema on our database and construct pedigrees in an attempt to determine the mode of inheritance. A secondary aim was to refine the phenotype by exploring the

prevalence of constant features within affected family members. In this way criteria for diagnosis could be established.

STUDY METHODS

All probands were identified from the tertiary-referral lymphedema clinic held at St. George's Hospital, London. All patients were referred with suspected lymphedema, highlighting the frequent misdiagnosis of these patients.

A thorough history was taken and examination performed for each proband. Once a clinical diagnosis of lipedema was made, by agreement of two specialists experienced in the diagnosis of lipedema, a full family history was taken and a pedigree constructed. As many family members as possible were interviewed and examined to confirm the presence or absence of a lipedema phenotype. Patients were excluded if they suffered from generalized obesity, primary, or secondary lymphedema (e.g., following cancer surgery) or any other condition leading to peripheral edema.

Demographic data were collected for all probands. They were asked their age of onset of lipedema and whether this coincided with the onset of puberty or pregnancy. The occurrence of easy bruising, skin tenderness, and other symptoms was recorded. The result of dieting upon limb swelling was ascertained.

Patients underwent a thorough clinical examination utilizing a standardized examination sheet (Fig. 1). Particular attention was paid to the presence of varicose veins, the signs of co-existent lymphedema if present, including the Kaposi–Stemmer sign. Weight and height were recorded to calculate BMI as well as waist-to-hip ratio. To confirm a symmetrical distribution, the patient's limb measurements were obtained with the patient standing, with legs parted to the same distance as their shoulders' width. Upper limb measurements were made with arms extended horizontally, palms facing upwards. The maximum circumference of thigh, lower leg, and upper arm bilaterally was recorded.

Data relating to all probands were entered into a database and DNA samples stored for possible use in future studies. Pedigrees were constructed for all probands with a proven family history of lipedema. The seven largest family pedigrees (with a minimum of three living affected members in at least two generations) are demonstrated in Figure 2.

Blood Extraction, Genotyping, and Linkage Analysis

Blood was taken in EDTA tubes for family Li05, and genomic DNA was extracted using standard protocols. For this family, a genome-wide scan was performed with the Illumina HumanLinkage-12 BeadChip (Illumina, Inc. 9885 Towne Centre Drive, San Diego, CA) consisting of 6,090 single nucleotide polymorphism (SNP) markers at an average distance of 0.58 cM. Processing of chips was performed according to the manufacturer's protocol. Bead chips were scanned using an Illumina Bead-station. Allele calls and their clustering were visually checked in Bead Studio and the Merlin plug-in was used to create input files for MERLIN.

All genotypes for the X-chromosome were checked for Mendelian inconsistencies in MERLIN (version 1.1.2) and deleted from

HISTORY	Yes	No	Comments
Age at diagnosis			
Age of onset			
Pubertal onset			
Easy bruising			
Pain at sites of swelling			
Painful knees			
Unsuccessful dieting			
Diabetes			
Hypertension			
EXAMINATION			
Swelling of feet			
Legs & hips affected			
Arms affected			
Fat pads			
Skin thickening			
Pitting of skin			
Varicose veins			
Stemmer sign positive			

Measurements :

Height (cm)

Weight (kg)

BMI.....

Waist Circ.....

Hips Circ.....

Right Thigh Circ.....

Right Lower Leg Circ

Left Thigh Circ

Left Lower Leg Circ

Right Upper Arm Circ

Left Upper Arm Circ

(Circ = maximum limb circumference)

FIG. 1. Standardized data sheet utilized during clinical examinations.

the pedigree file using the PEDWIPE function. A parametric linkage test was run using the MINX function. As MINX is unpublished the results were checked using the MERLIN function and adding sex-specific penetrances to the model file.

STUDY RESULTS

Inheritance

In the consecutive series, a total of 330 family members were identified, comprising 67 propositi and their affected and unaffected family members. Ten of the 67 propositi had at least one first-degree relative with confirmed lipedema. This provides a minimum familial incidence of 15% with (10/67) of propositi having a positive family history. Seven of the propositi had at least two other affected first-degree relatives. All affected family members were female first- or second-degree relatives of female propositi. Of note, there was no history of infertility or increased miscarriage rate reported by the patients.

Of the seven pedigrees demonstrated in Figure 2, one family had six living affected members in three generations, two families had

five affected members, two had four affected members, and one further family had three living affected members.

Family Li05 was investigated for possible X-linked dominant inheritance as it was the largest pedigree, and lod scores of below -2 were returned for all X chromosome markers.

Phenotypic Features

All 67 propositi were examined by two of the trained observers (P.M., A.C., P.S., G.B.), who both agreed the diagnosis. Of the 67 propositi, 38 were examined by the most experienced author (P.M.), including the patients of the seven illustrated families with multiple affected members. Complete information was available for all 38 female propositi age range 26–74 years, mean age 51 years. We noted the following results:

- (i) *Age of onset.* The onset of lipedema occurred during puberty in 21 cases (55%).
- (ii) *Effect of diet.* Thirty-six of the 38 propositi (96%) reported that dieting failed to reduce weight below the waist, while successfully reducing fat deposition on the face, neck, and upper

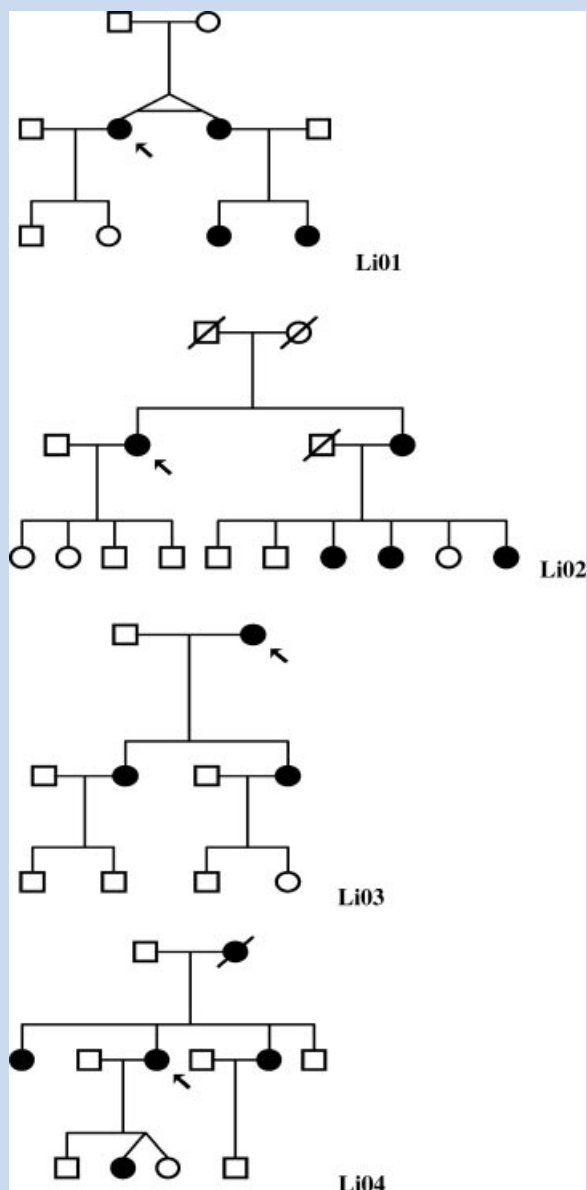


FIG. 2. Pedigrees of families with lipedema suggesting an autosomal dominant mode of inheritance.

trunk. Dieting therefore increased the disproportionate distribution of body fat.

- (iii) *Pain*. Twenty-seven out of 38 probands (71%) reported that swollen legs were painful upon pressure. Thirty-one (82%) reported easy bruising. Knee pain was a common complaint, affecting 21 (55%), age range 23–82, mean age 50.8 years. Knee pain is a feature of lipedema, but can also be found in simple obesity. Nevertheless, it appears to be a phenotypic feature and is often a complaint in pure lipedema where the BMI is normal.
- (iv) *Body mass index*. The BMI range for the probands was 21.1–54.6. Four percent of patients scored a WHO classification of having a “normal” weight (BMI = 18.5–24.99). Eleven

percent were classed as “overweight or pre-obese” (BMI = 25–29.99). Eight percent of probands were in the “obese class I” group (BMI = 30–34.99). Twenty-seven percent were in the “obese class II” group (BMI 35–39.99) and 50% of probands were in “obese class III” (BMI = ≥ 40) [WHO “BMI calculation,” 2010b].

- (v) *Varicose veins*. Fifteen patients had associated varicose veins clinically (39.5%), while 20 (53%) had venous telangiectasia/reticular veins on their legs.
- (vi) *Fat pads*. Twenty-two probands (58%) had fat pads around the knees. Such fat pads were bulging protuberances of fat either immediately above the knee or immediately below (inferomedial) the knee, that is, pre-tibial fat pads.

Based upon our findings, we designed a table comparing the phenotypic features of lipedema and lymphedema (see Table I).

DISCUSSION

The familial nature of the condition suggests that lipedema can demonstrate heritability. The exact nature of the form of inheritance is difficult to determine, and a segregation analysis with no affected males or males that demonstrate transmission to affected females, would yield no meaningful data. The pedigrees are consistent with either X-linked dominant inheritance or autosomal dominant inheritance with sex limitation, but there could be oligogenic inheritance. Linkage analysis with X chromosome markers for family Li05 gave lod scores that excluded all markers on this chromosome. Thus, autosomal dominant inheritance is the more likely mode of inheritance.

Sex-limited dominant conditions are uncommon, especially for single gene disorders, but two examples would be Female Restricted Epilepsy with Mental Retardation (OMIM 300088) and Male Limited Precocious Puberty (OMIM 176410). The former shows X-linked dominant inheritance, and the causative gene is protocadherin 19 [Dibbens et al., 2008]. The latter condition is inherited in an autosomal dominant manner, and is due to mutations in the gene that codes for the receptor for luteinizing hormone [Schedewie et al., 1981; Shenker et al., 1993]. Examples of sex-limited conditions also include male pattern baldness (OMIM 109200) [Hamilton, 1951; Hillmer et al., 2002], which may be due to a single gene, though oligogenic inheritance is more likely.

Separately from the present reported series, in our consecutive clinic population we have identified four unrelated isolated adult males with lipedema. One proband had liver disease, gynaecomastia, and signs of estrogen excess. Another suffered from growth hormone deficiency and hypogonadism. The remaining two patients were testosterone-depleted. None of the male probands were syndromic, nor did they have a family history of lipedema. We propose that these males developed lipedema secondary to hormonal disturbances, with reduced testosterone levels being a common factor.

One of the problems in recruiting families is recognition of the phenotype. The diagnosis is currently clinical with no absolute phenotypic feature or confirmatory test. Many patients with lipedema develop obesity (Latin *obesus* “grown fat by eating”) making

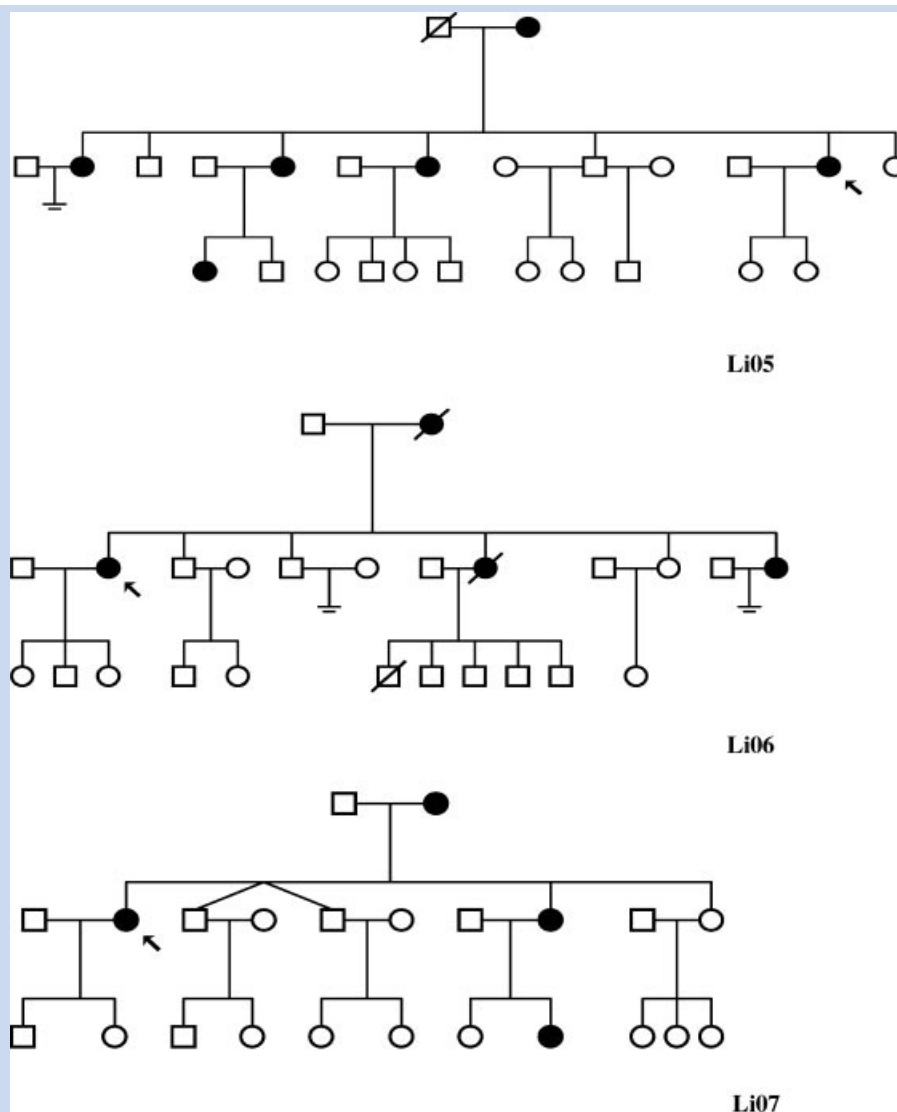


Fig. 2. (Continued)

distinction between lipedema and obesity difficult. It is therefore only strictly in a thin person with disproportionately large buttocks, hips, thighs, or legs where the diagnosis can be assured, or in an overweight female where successful weight loss from dieting has no effect on lower limb size. Indeed, many lipedema patients choose not to diet because of the effect it has on emphasizing the disproportionate distribution of body fat.

Another consideration in differential diagnosis has to be rarer forms of lipodystrophy where there may be loss (lipoatrophy) or gain (lipohypertrophy) of subcutaneous fat. Many of the lipodystrophies are associated with abnormalities of glucose/insulin metabolism or have other syndromic features.

As lipedema appears to be expressed most commonly at puberty, it is reasonable to assume that hormonal influence underlies the marked female limitation shown in our studies to date and also reported by Kroger [2008]. The possibility of male lethality with the mutation does need to be considered. There is an excess of females to males born to affected females (29 F:18 M) but this is not

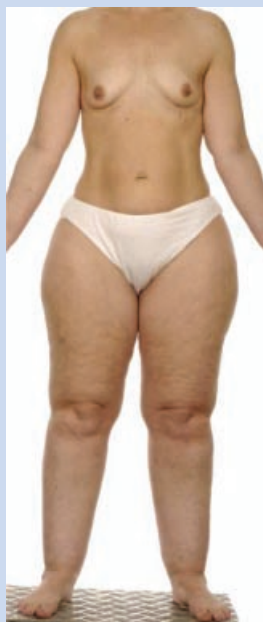
significant ($P = 0.108$). The relatively benign phenotype in females coupled with the pubertal onset of clinical signs would suggest a hormonal influence on phenotype as the most likely scenario, but a P -value approaching 0.1 for a skewed offspring ratio means that male lethality cannot be ruled out, despite the lack of miscarriage history in our probandi. It will thus be extremely useful to continue ascertaining as many families as possible for future genetic linkage and biochemical studies on this disorder. Such data will allow the causative gene to be identified, increasing our understanding of the generation of obesity, and stimulating the search for rational therapy for this often very distressing condition.

ACKNOWLEDGMENTS

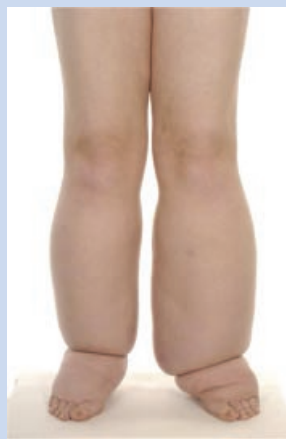
The authors A.C., P.S., and G.B. wish to thank the Bluff-Field Charitable Fund, St. George's, University of London and St. George's NHS Hospital Trust for their support. P.O. was funded by the Daphne Jackson Trust and by the British Skin Foundation.

TABLE I. Comparison of the Phenotypic Features of Lipedema, Lymphedema, and Obesity

Characteristic	Lipedema	Lymphedema	Obesity
Sex	Females only	Males and females	Female dominance
Age of onset	Puberty	Any decade	Any decade
Family history	Approximately 15% of cases	Present in approximately 20% of cases of primary lymphedema [Dale, 1985]	65% based on twin studies
Symmetry	Bilateral and usually symmetrical, but may be asymmetrical	Bilateral or unilateral	Symmetrical (android or gynoid ^a)
Swollen feet	Never (initially)	Usually	Never
Skin consistency	Normal	Thicker and firmer	Normal
Pitting of skin	Absent (initially)	Present	Absent
Easy bruising of affected areas	Often	No increased incidence	Absent
Pain and discomfort of affected areas	Often	Infrequent	Absent
Tenderness of affected areas	Often	Infrequent	Absent
Effect of dieting	No effect on legs	Even loss from trunk and legs	Symmetrical loss from affected areas commencing with the face and descending gravitationally



Lipedema of the lower limbs. Note the “inverse shouldering” effect above the ankles due to sparing of the feet



Bilateral lower limb primary lymphedema. Note involvement of the dorsal aspect of the feet



Central “android” obesity in a female. Illustration courtesy of Professor S. Nussey, St. George’s Hospital

Adapted from a table proposed by Wold et al. [1951].

^aAndroid, centralized, or “apple-shaped” obesity; gynoid, generalized, or “pear-shaped” obesity.

“The linkage data was generated using the facilities of the St. George’s Biomics Unit.”

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