Case Report

Body fat distribution in women with familial partial lipodystrophy caused by mutation in the lamin A/C gene

Luciana Z. Monteiro, Maria C. Foss-Freitas, Renan M. Montenegro Júnior[1], Milton C. Foss

Department of Medicine, Divisions of Endocrinology and Metabolism, Ribeirão Preto Medical School, São Paulo University, Brazil, [1]Department of Community Health, Service of Endocrinology and Diabetes, University Hospital Walter Cantídio, Fortaleza Medical School, Ceará University, Brazil

ABSTRACT

Familial partial lipodystrophy (FPLD), Dunnigan variety, is an autosomal dominant disorder caused due to missense mutations in the lamin A/C (LMNA) gene encoding nuclear lamina proteins. Patients with FPLD are predisposed to metabolic complications of insulin resistance such as diabetes. We sought to evaluate and compare body fat distribution with dual-emission X-ray absorptiometry in women with and without FPLD and identify densitometric, clinical and metabolic features.

Key words: Body composition, familial partial lipodystrophy, profile metabolic, women

Introduction

Lipatrophic diabetes, also referred to as familial partial lipodystrophy (FPLD), is a rare disease that is metabolically characterized by hypertriglyceridemia and insulin resistance. Affected patients typically present with regional loss of body fat and muscular hypertrophic appearance. Variable symptoms may comprise pancreatitis and/or eruptive xanthomas due to severe hypertriglyceridemia, acanthosis nigricans and polycystic ovaria.[1] Mutations within the lamin A/C (LMNA) gene on chromosome 1q21.2 were recently reported to result in the phenotype of FPLD.[2] The purpose of this study was to evaluate and compare body composition with dual-emission X-ray absorptiometry (DEXA) in 14 women with and without FPLD and identify densitometric, clinical and metabolic features.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.91209

Case Report

The study was conducted in Clinic of Endocrinology and Metabolism, with five families with FPLD. Patients signed an informed consent, and the ethical committee of the institution approved this study. We found mutations within exon 8 of LMNA (R482W), in 13 women with FPLD and in exon 11 (R644C) in 1 woman. The mean age of the patients with FPLD was 35.8±13.9 years and of those without FPLD was 35.9±13.8 years. A group of 14 healthy women who matched for age, height, weight and body mass index (BMI) were recruited as controls. These subjects had a normal fat distribution, belonged to the same ethnic origin and did not show a family history of lipodystrophy.

All patients were submitted to clinical evaluation by anamnesis and to general physical examination with the analysis of signs and symptoms suggestive of partial familial lipodystrophy. The family history was considered to be suggestive of lipodystrophy when there were first-degree relatives with a diagnosis of diabetes and/or coronary disease and/or consanguinity and/or the existence of relatives with a similar phenotype.

Corresponding Author: Dr. Luciana Zaranza Monteiro, Department of Medicine, Ribeirão Preto Medical School, São Paulo University of São Paulo, Av. Bandeirantes, 3900, Monte Alegre, Ribeirão Preto (SP), Brazil, 14049-900. E-mail: lucianazaranza@usp.br

The distribution of subcutaneous fat in the trunk, face, cervical region and upper and lower limbs was evaluated by ectoscopy and palpation, with the patient in her underwear. During physical examination, muscular pseudohypertrophy of upper and lower limbs, prominent venous vascularization and cervical and axillary acanthosis nigricans were actively investigated in the women, as well as the presence and degree of acne and hirsutism.

Blood was collected after a 12-hour overnight fast for the analysis of serum lipoproteins, insulin, glucose, and a chemistry profile.

Whole-body DEXA scans were obtained with Hologic 4500 W, USA. Wilcoxon exact tests were also used to compare densitometric, clinical and metabolic features in women with and without FPLD. *P* value <0.05 was considered statistically significant.

Genetic studies

Screening for mutations of LMNA was done through direct sequencing Genomic DNA was extracted from peripheral blood, with the kit QIAamp DNA Blood (Qiagen, Valencia City,CA, USA). The amplification of LMNA gene was designed to include the exon-intron junction, allowing the screening for mutations at alternative splicing sites. The primers used to amplify exons 8 and 9 were previously described.[2] Primers used in exon 11 analysis were designed as follows: primer forward 5',GTAGCTAGAACAGAGTCAGAGTC 3', primer reverse 5', AGAGAGAAAACAGAGGAGAGAGG 3',. DNA sequencing was performed on ABI3130 Genetic Analyzer (PE Applied Biosystems, Foster City, CA, USA), using BigDye® Terminator Cycle Sequencing Kit V3.1 Ready Reaction (ABI PRISM/PE Biosystems, Foster City, CA, USA). Results were analyzed using the *Condon Code Aligner* software (Li-COR, Inc.), following manufacturer's instructions.

The relevant results are depicted in Table 1. We observed significant differences in laboratory tests and the distribution of body composition. All patients with FPLD exhibited hepatic steatosis in magnetic resonance imaging (MRI), muscle hypertrophy, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol.

Table 1: General characteristics, biochemical parameters and dual-energy X-ray absorptiometry of female patients with familial partial lipodystrophy, Dunnigan variety

Test	Women with FPLD (n = 14)	Control (n = 14)	*P*
Fasting glucose (70–100 mg/dl)	140.9 ± 76.7	76.21 ± 3.8	<0.01
Insulin (μU/ml)	36.3 ± 29	3.3 ± 1.3	<0.01
AIC (%)	7.8 ± 2.5	5.3 ± 0.4	<0.01
Cholesterol (mg/dl)			
Total (<200)	201.8 ± 51.8	181.36 ± 45.1	0.32
HDL (>45)	38.4 ± 6	49.3 ± 10.5	<0.01
Triglycerides (<150 mg/dl)	302.1 ± 177.4	84 ± 27	<0.01
Uric acid (2.4–5.7 mg/dl)	5.5 ± 1.4	3.6 ± 0.8	<0.01
ALT (10–37 mg/dl)	49.1 ± 41.3	15.8 ± 4.7	<0.01
AST (10–37 mg/dl)	42.8 ± 31.1	19.4 ± 3.8	0.01
CRP (mg/dl)	0.5 ± 0.5	0.1 ± 0.2	0.02
CPK (U/l)	144.9 ± 74.4	76.4 ± 22.7	<0.01
DEXA			
Height (m)	1.6 ± 0.1	1.6 ± 0.1	0.91
Weight (kg)	58.6 ± 5.9	63.9 ± 6.7	0.99
BMI (kg/m^2)	23 ± 2.1	23.2 ± 2.4	0.82
Fat (%)			
Total	19.1 ± 4.2	34.8 ± 5.1	<0.01
Trunk	23.6 ± 5.1	31.2 ± 6.3	<0.01
Fat mass (kg)	10.1 ± 2.3	19.1 ± 4.1	<0.01
Total	6.73 ± 1.6	8.6 ± 2.5	0.04
Trunk			
Lean mass (kg)			
Total	41.4 ± 4.5	34.1 ± 3.9	<0.01
Trunk	21.2 ± 2.2	18.1 ± 1.8	<0.01

Data are means ± SD, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BMI: Body mass index, CPK: Creatine phosphokinase, CRP: C-reactive protein, FPLD: Familial partial lipodystrophy, Dunnigan, DEXA: Dual-energy X-ray absorptiometry

Discussion

FPLD (MIM 151660) is a rare autosomal dominant form of insulin resistance caused by mutant LMNA, which encodes nuclear lamin A/C, a structural component of the nuclear envelope.[3] FPLD is characterized by loss of fat affecting the limbs and trunk, accumulation of fat in the neck and face, and predisposition to insulin resistance, leading to complications such as glucose intolerance, dyslipidemia, high blood pressure, liver steatosis, and increased risk for coronary heart disease. Because of the gradual loss of subcutaneous adipose tissue within arms and legs, these limbs appear to be unusually muscular.[4]

The LMNA gene encodes two nuclear proteins, lamin A and C, which are the essential structural components of most differentiated mammalian cells. Rare mutations in exon 8 of LMNA cause the autosomal-dominant Dunnigan-type FPLD.[5] In later life, individuals with FPLD often experience severe metabolic derangements, including insulin resistance, dyslipidemia, heart disease, and type 2 diabetes. Mutations elsewhere in the LMNA gene are associated with several additional autosomal- dominant diseases.[6]

In our study, lack of adipose tissue was particularly noticeable in trunk in women with FPLD. MRI studies confirmed the clinical findings of excess of adipose tissue in the face, neck, chin, axillae, and labia majora. Although

Jackson *et al*.;[7] had concluded, in their study of two patients with FPLD, that there was a total lack of subcutaneous fat in all areas except the cheeks, palms and soles, their published MRI of head, thorax, and abdomen showed that subcutaneous fat was present in these areas.

Patients with FPLD also need to be distinguished from the less common Kobberling variety of FPL. On the basis of clinical findings, the loss of adipose tissue in the Kobberling variety is said to be restricted to extremities only.[8,9] Patients have normal amounts of fat in the face area and may have normal, or even excess, subcutaneous fat in the truncal area.

Only recently, DEXA has been used for body composition estimation. There are few studies describing its use in lipodystrophic patients.[10] Compared with patients with FPLD, those without FPLD tended to have less severe metabolic complications; their fasting serum triglyceride concentrations were lower and HDL cholesterol concentrations were higher.

Identification of the FPLD gene will further our understanding of the pubertal growth and differentiation of adipose tissue and how the gene defect results in the characteristic adipose tissue distribution.

In conclusion, on comparing women with FPLD and without FPLD, the affected women have a difference pattern of loss of subcutaneous adipose tissue from the trunk and are more severely affected with metabolic complications. In this study, DEXA measurements of fat distribution helped to better characterize the lipodystrophy. Further studies with larger series are necessary to improve the strategies in the diagnosis of lipodystrophies.

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Cite this article as: Monteiro LZ, Foss-Freitas MC, Montenegro RM, Foss MC. Body fat distribution in women with familial partial lipodystrophy caused by mutation in the lamin A/C gene. Indian J Endocr Metab 2012;16:136-8.

Source of Support: Nil, **Conflict of Interest:** None declared.