Endocr (2009) 35:18–21
DOI 10.1007/s12020-008-9127-1

CASE STUDY

A case of Dunnigan-type familial partial lipodystrophy (FPLD) due to lamin A/C (*LMNA*) mutations complicated by end-stage renal disease

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Received: 22 July 2008 / Accepted: 13 October 2008 / Published online: 15 November 2008
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Abstract Dunnigan-type familial partial lipodystrophy (FPLD) is a rare monogenic adipose tissue disorder in which the affected subjects have increased predisposition to insulin resistance and related metabolic complications, such as glucose intolerance, diabetes, dyslipidemia, and hepatic steatosis**.** Our patient was a 35-year-old female who had been receiving insulin injection therapy for diabetes mellitus and was transferred to our hospital. She was diagnosed with FPLD on the basis of the following symptoms: increase in subcutaneous fat in the face, neck, and upper trunk; loss of subcutaneous fat in the lower limbs and the gluteal region. We found a heterozygous CGG to CAG transition in codon 482 of exon 8 in the gene encoding lamin A/C (*LMNA*), which leads to an arginine to glutamine substitution (R482Q). At the time of admission, her serum creatinine level was 8.4 mg/dl, and her blood urea nitrogen (BUN) level was 81 mg/dl. Her serum creatinine level was elevated and hemodialysis was performed twice every week. However, she died of cerebral hemorrhage 9 months after hemodialysis. Although it is uncommon for patients with FPLD to exhibit renal dysfunction and require hemodialysis, this case suggests the need for careful analysis of renal function in a patient with FPLD.

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Keywords Familial partial lipodystrophy · Lamin A/C · LMNA · Diabetes mellitus · Renal dysfunction

Introduction

Dunnigan-type familial partial lipodystrophy (FPLD) is a rare monogenic adipose tissue disorder in which the affected subjects have increased predisposition to insulin resistance and related metabolic complications, such as glucose intolerance, diabetes, dyslipidemia, and hepatic steatosis [1–5]. Patients with FPLD are healthy at birth, but around puberty they lose fat stores selectively from the extremities and gluteal region, while visceral, facial, and neck fat content is preserved and may increase with caloric excess [3]. The disorder is inherited in an autosomal dominant fashion and has been attributed to missense mutations in the gene encoding lamins A and C (*LMNA*) on chromosome 1q21-22 [6–9]. Lamins A and C belong to the family of intermediate filament proteins and are structural components of the nuclear lamina. Garg [10] reported that compared to men affected with FPLD, women with FPLD are particularly predisposed to diabetes. Among FPLD kindreds, *LMNA* mutation carriers, particularly women, had a very high risk of early coronary heart disease (CHD) as compared with familial controls [11]. However, the risk factors that predispose patients with FPLD to diabetes remain unclear.

In this report, we present the case of a 35-year-old woman who had an *LMNA* R482Q mutation and was diagnosed with diabetes mellitus with severe insulin resistance, hypertension, dyslipidemia, and progressive renal failure.

Case report

A 35-year-old woman suffering from progressive renal failure was admitted to our hospital to induce a hemodialysis. At the age of 8 years, she was diagnosed with diabetes mellitus at a hospital in her neighborhood. Insulin injection therapy was initiated when she was 13 years old, and the dosage of insulin was increased up to 100 units/day. She was transferred to our hospital for evaluation of her diabetes mellitus when she was 19 years old. We noted an increase in subcutaneous fat in the face, neck, and upper trunk and a loss of subcutaneous fat in the lower limbs and gluteal region (Fig. 1). She had developed facial hirsutism and acanthosis nigricans in the axillary folds. The external genitalia showed moderate labial hypertrophy and clitoromegaly. Her menarche was at the age of 11 years old, and then she subsequently developed oligomenorrhea. However, a gynecologist in our hospital denied a diagnosis of polycystic ovary syndrome. Her father had been diagnosed with diabetes mellitus but did not display any physical symptoms of lipodystrophy. We found a heterozygous CGG to CAG transition in codon 482 of exon 8 in *LMNA* (data not shown), which leads to an arginine to glutamine substitution (R482Q). This DNA variation has been previously reported [6–9]. The patient was diagnosed with FPLD2, and her glycemic control was improved by multiple insulin injection therapy, with the HbA1c values ranging from 6.5% to 7% for approximately 10 years. During the course of this administration, she was diagnosed with renal dysfunction. At first, a microalbuminuria was pointed out at 24 years of age. The elevation of serum creatinine was noted when she was 30 years old. At the time of admission, she was 161 cm tall, weighed 59.5 kg and body mass index 23%. Her blood pressure was 150/90 mmHg, and she had normal sinus rhythm. Pitting edema was present in both legs due to chronic renal failure with hypoproteinemia. Optical fundoscopic findings showed hemorrhagic changes. At the time of admission, her serum creatinine level was 8.4 mg/dl, and her blood urea nitrogen (BUN) level was 81 mg/dl. The serum total protein and albumin levels were 5.6 g/dl and 3.1 g/dl, respectively. She had a hemoglobin level of 7.2 g/dl, a hematocrit (Ht) level of 22%, a white blood cell count of 8,470/μl, a platelet count of 192,000/μl, a fasting plasma glucose level of 119 mg/dl, and an HbA1c level of 6.3% (Table 1). Liver function and the levels of serum total hemolytic complement and its C3 and C4 fractions were normal. Echocardiography and 24 h electrocardiogram monitoring showed no abnormalities. An abdominal echogram showed a bilateral renal atrophy. Urinary analysis showed massive proteinuria (3+), 50–99 red blood cells per high-power field (HPF), and hyaline cast and granular casts in the urinary sediment. This finding is suggestive of a glomerular disease. Tests for antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic antibodies, cryoglubulins, antibodies to hepatitis B and C virus were all negative. An abdominal echogram showed a bilateral renal atrophy. Further examinations were not done because renal biopsy or autopsy was not performed.

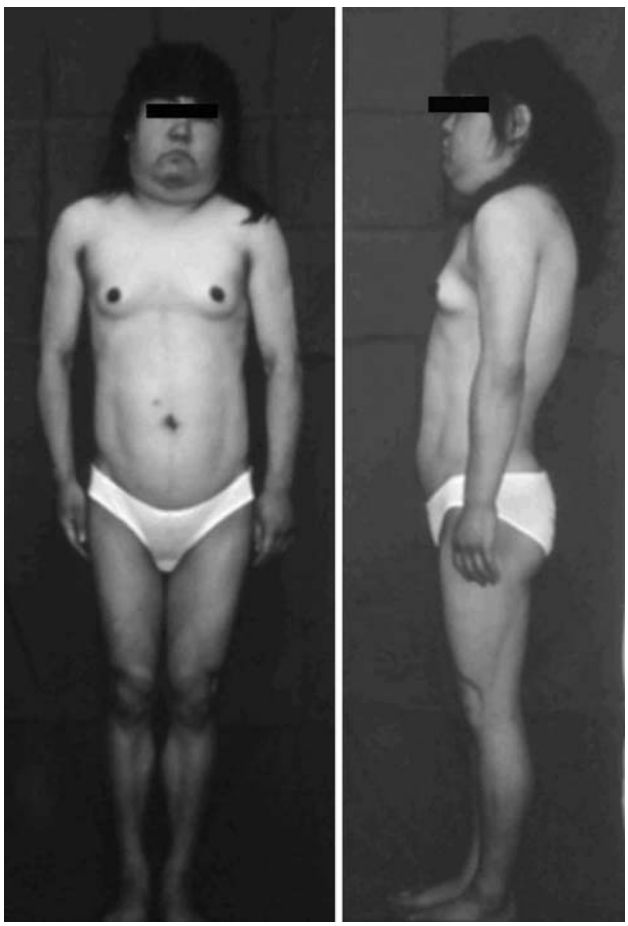

Fig. 1 Clinical spectrum of FPLD in the patient. The patient has a cushingoid face and a lack of subcutaneous fat in the abdomen

The patient was placed on a diet consisting of low protein (40 g/day), low salt (6 g/day), diuretics, and was advised bed rest. However, her serum creatinine level increased, and subsequently, hemodialysis was performed twice every week. In spite of this, she died of cerebral hemorrhage 9 months after hemodialysis.

Discussion

We report a case of progressive renal failure in a diabetic patient with FPLD. The diagnosis of FPLD was established by symmetrical lipoatrophy of the trunk and limbs, with a rounded, cushingoid face with excess accumulation of fat on the face, neck, and supraclavicular areas. As previously reported, lipodystrophy was associated with severe insulin

Table 1 Laboratory data on admission

Blood chemistry	
CRP	0.1 mg/dl
TP	5.6 g/dl
ALB	3.1 g/dl
BUN	81 mg/dl
CRE	8.4 mg/dl
UA	7.4 mg/dl
T-Bil	0.3 mg/dl
GOT	13 U/l
GPT	6 U/l
ALP	152 U/l
LDH	373 U/l
γGPT	10 U/l
Cholinester	417 U/l
AMY	90 U/l
Na	137 mmol/l
K	4.3 mmol/l
Cl	10.3 mmol/l
Ca	7.6 mg/dl
Phosphorus	6.6 mg/dl
TCHO	194 mg/dl
TG	307 mg/dl
HDLC	30 mg/dl
FBS	119 mg/dl
HbAlc	6.3%
Blood count	
WBC	8470/μl
RBC	2.65×10^4/μl
Hb	7.2 g/dl
Ht	22%
MCV	83 fl
MCH	27.2 pg
MCHC	32.7%
Plt	192×10^4/μl
Urinalysis	
Glucose	(−)
Protein	(3+)
Sediment	
RBC	50–99/hpf
Casts	Hyaline cast
	Granular cast

resistance and acanthosis nigricans [10]. Our patient displayed typical features of FPLD.

FPLD is an autosomal dominant disorder caused by missense mutations in the *LMNA* gene encoding nuclear lamina proteins. It is characterized by a loss of subcutaneous fat from the extremities and trunk and accumulation of fat in the head and neck region beginning at puberty [1]. Patients with FPLD are predisposed to metabolic complications of insulin resistance, such as diabetes. Previous reports have shown that compared with men affected with FPLD, women with FPLD are particularly predisposed to diabetes [10]. However, the risk factors that predispose patients with FPLD to diabetes remain unclear. For example, it is not clear whether a particular *LMNA* mutation, the degree of fat loss from the extremities and trunk, or the excess fat deposition predisposes patients to diabetes. It has been concluded that women with FPLD are more predisposed to diabetes than men [12]. This tendency among women may be due to increased adiposity in regions unaffected by lipodystrophy, as reflected by increased submental deposition of subcutaneous fat. Furthermore, parity may predispose women with FPLD to diabetes. Age, menopausal status, familial history of type 2 diabetes, and *LMNA* variants do not predict predisposition to diabetes. Our patient was female and showed severe insulin resistance. The incidence of cerebral hemorrhage in patients undergoing hemodialysis (HD) is approximately 5–10 times higher than that in the general population [13]. Our patient died of the cerebral hemorrhage. There is no report that the diagnosis of FPLD2 had any connection to the cerebral hemorrhage. Further investigations are needed to clarify the relationship between FPLD2 and cerebral hemorrhage.

A-type lamins are formed by the alternative splicing of the mRNA of the *LMNA* gene, which is located in chromosome 1q 21–22; the main isoforms of these proteins are lamins A and C [14]. A-Type lamins belong to the family of intermediate filament proteins and are ubiquitously expressed in most differentiated tissues. Once transported into the nucleus, they co-polymerize with B-type lamins to form the nuclear lamina, a meshwork located on the inner aspect of the nuclear envelope. The attachment of the lamina to the membrane is mediated by transmembrane nuclear proteins, including emerin, which binds A-type lamins through its nucleoplasmic domain [15]. The structure of the lamins comprises a centralhelical dimerization domain flanked by an amino-terminal region (head) and a carboxyl-terminal region (tail) [16]. Naturally occurring mutations in *LMNA* have been shown to be responsible for six distinct diseases called laminopathies: autosomal dominant and recessive Emery-Dreifuss muscular dystrophy (EDMD) [17, 18], limb-girdle muscular dystrophy type 1B (LGMD1B) [19], dilated cardiomyopathy with conduction defects (DCM-CD) [20], autosomal recessive Charcot-Marie-Tooth disease type 2 (CMT2B1) [21], FPLD [6–8, 22], and mandibuloacral dysplasia (MAD) [23]. FPLD is caused by a few specific heterozygous nucleotide substitutions leading to amino acid changes in the carboxyl-terminal domain of lamin A/C; more than 90% of the mutations affect the 482nd codon of the gene [6–8, 22].

Previous reports indicated that membranoproliferative glomerulonephritis (MPGN) type 1 and type 2, focal segmental glomerulosclerosis, and diabetic nephropathy were

observed in lipodystrophy [24]. MPGN type 2 was also identified in one patient with FPLD2 who did not have low C3 levels [25]. Further, in a previous study, five out of six FPLD2 patients had microalbuminuria, while one had macroalbuminuria associated with chronic renal insufficiency, hypertension, and diabetes; however, renal biopsy was not performed [24]. Although our patient was diagnosed with progressive renal failure, we could not identify its cause. Renal failure in our patient could have been caused by several factors: [1] diabetic nephropathy; the patient had a history of diabetes mellitus in spite of normal levels of blood glucose and [2] MPGN; the patient may have had MPGN but this was not confirmed since we did not perform renal biopsy or autopsy. A more detailed analysis is required to determine the relationship between FPLD2 and renal failure.

In conclusion, we report a patient who suffered from FPLD2 along with diabetes mellitus and progressive renal failure. She is the first patient with FPLD2 to receive hemodialysis.

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