Journal of Clinical Lipidology (2016) 10, 1488–1491

Journal of Clinical Lipidology

Case Study

Familial partial lipodystrophy presenting as metabolic syndrome

Darwin Chan, BA, MS, Adam D. McIntyre, HBSc, Robert A. Hegele, MD, Andrew C. Don-Wauchope, MBBCh, MD*

School of Medicine, McMaster University, Hamilton, Ontario, Canada (Dr Chan); Vascular Biology Group, Robarts Research Institute and Department of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada (Drs McIntyre and Hegele); Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada (Dr Don-Wauchope); and Lipid Clinic, Hamilton General Hospital, Hamilton, Ontario, Canada (Dr Don-Wauchope)

KEYWORDS:
Dunnigan-type 2 familial partial lipodystrophy;
FPLD2;
Lamin A/C;
Metabolic syndrome

Abstract: We report the first described case of a heterozygous p.R545H (c.1634 G > A) missense mutation in the *LMNA* gene with clinical features compatible with Dunnigan–type 2 familial partial lipodystrophy (FPLD2). The case presented as metabolic syndrome to a specialist clinical service and highlights the overlap between FPLD2 and the metabolic syndrome. The associations with type 2 diabetes mellitus, fatty liver disease, polycystic ovarian syndrome, and hypertriglyceridemia are highlighted. The importance of evaluating patients for these associated conditions is discussed, and the potential mechanisms of disease are briefly outlined. The mutation has been previously reported in a heart failure database without a clinical description. The links between heart failure and the clinical condition are briefly considered.

Background

Lipodystrophies may manifest in a variety of ways including a clinical presentation similar to that of metabolic syndrome.[1] They are a rare heterogeneous group of disorders characterized by generalized or selective lipoatrophy of adipose tissue and are often diagnosed late. This heterogeneous group includes familial partial lipodystrophy, a sub-type of which is autosomal dominant Dunnigan-type 2 familial partial dystrophy (FPLD2; MIM: 151600). Patients with FPLD2 are born with normal fat distribution but lose subcutaneous fat from their extremities, trunk, and gluteal region after the onset of puberty.[2,3] Excess fat deposits may be seen at the neck, face, and intra-abdominal region,[2,3] resulting in a cushingoid appearance. The metabolic syndrome, a constellation of derangements including dyslipidemia, hypertriglyceridemia, hyperglycemia, insulin resistance, hepatic steatosis, increased central adiposity, increased cardiovascular risk, and increased type 2 diabetes risk, is common in patients with lipodystrophy.[1] Approximately 20 to 33 percent of FPLD2 patients have acanthosis nigricans, hirsutism, menstrual abnormalities, and polycystic ovaries.[4] The locus for FPLD2 was reported to be on chromosome 1q21-22.[5] Several missense mutations have been reported in patients with FPLD2 in the *LMNA* gene[6] that encodes nuclear lamin A and C. We report a woman presenting to a cardiac prevention clinic with typical features of metabolic syndrome who was found to have FPLD2 with a rare *LMNA* mutation.

* Corresponding author. Lipid Clinic, Hamilton General Hospital, 237 Barton Street, Hamilton, L8L 2X2, Ontario, Canada.
E-mail address: donwauc@mcmaster.ca
Submitted June 19, 2016. Accepted for publication August 19, 2016.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2016.08.012

Case report

A 51-year-old woman was referred to the Cardiovascular Risk Reduction Clinic presenting with an abnormal lipid profile. Her prior medical history included hypercholesterolemia with no hypertension or diabetes, but at the time, she reported that her blood glucose and blood pressure were rising over the past three years with concomitant changes in her body habitus. She was previously diagnosed with polycystic ovaries with oligomenorrhea and reported some excessive hair on her torso and legs. She had no family history of cardiovascular disease, diabetes, or lipodystrophy, but she reported that her son had high blood cholesterol. She stated that she smoked a pack of cigarettes a day. Current medications included toradol 10-mg PRN, amitriptyline 75-mg OD, ezetimibe 10-mg OD, quinine 300-mg OD, and propranolol 20-mg OD. She had discontinued atorvastatin because of elevations of her transaminases.

On physical examination, she had a lipodystrophic habitus with lipoatrophy of her limbs and buttocks, central adiposity with some subcutaneous fat over her abdominal muscles, and increased fat deposits in the anterior supraclavicular regions of the neck and along the jawline, giving her a double chin. Her calves appeared to be lean and muscular. She did not have hirsutism. She was 162 cm tall, her weight was 61.1 kg, her body mass index (BMI) was 23.1 kg/m^2, her waist circumference was 93 cm, and her blood pressure was 114/84 mm Hg with a pulse of 80 bpm. Her cardiac and respiratory examinations were normal. The patient did not have hepatomegaly on clinical examination.

Her laboratory results included the following: fasting plasma glucose, 5.5 mmol/L (normal range, 4.0–6.0 mmol/L); total cholesterol, 8.23 mmol/L (4.3–6.5 mmol/L); triglycerides, 5.95 mmol/L (0.67–3.15 mmol/L); and HDL-C, 1.08 mmol/L (1.0–2.4 mmol/L). Her alanine transaminase level was slightly elevated at 39 U/L (3–36 U/L). Her creatine kinase level was normal at 50 U/L (5–130 U/L). Previous investigations for metabolic and viral liver diseases were all negative. HbA1c was not measured at the time.

Genomic DNA from whole blood was amplified using specific *LMNA* primers. We bi-directionally Sanger sequenced *LMNA* coding regions and intron-exon boundaries using the same primers on a model 3730 Automated DNA Sequencer (Applied Biosystems, Mississauga, ON) at the London Regional Genomics Centre (www.lrgc.ca). DNA sequences were analyzed using Seq Scape, v2.6 (Applied Biosystems, Foster City, CA). The patient was found to carry a rare heterozygous mutation, p.R545H (c.1634 G > A), in the *LMNA* gene; the variant frequency was 0.00018 in the ExAC database, but no phenotypic information is provided. The variant has reference number rs142191737 and was predicted to be deleterious by SIFT and PolyPhen software. Her two sons were consented to have genetic testing with negative results for *LMNA* mutations. Because no other relatives agreed to be tested, it is not possible to determine whether the mutation is de novo.

Two months later, an oral glucose tolerance test revealed an elevated glucose of 12.7 mmol/L (<11.1 mmol/L) at 2 hours indicating type 2 diabetes. A computed tomography scan of her abdomen a year later revealed mild fatty infiltration of the liver with hepatomegaly. An epicardial fat assessment via transthoracic echocardiography demonstrated an elevated amount of epicardial fat when compared to a research database matched for age, gender, and BMI. Other echocardiographic parameters were reported as normal. Owing to the presence of mixed dyslipidemia, the patient was treated with fenofibrate and given lifestyle management advice including diet, exercise, and smoking cessation recommendations.

Discussion

This case demonstrates the need for awareness of lipodystrophies in patients seen in lipid clinics or cardiovascular prevention clinics, and more importantly, the similarity in clinical features of lipodystrophies such as FPLD2 to metabolic syndrome. Molecularly proven partial lipodystrophy, specifically due to heterozygous mutations in *LMNA* has been documented in 10% of patients with severe metabolic syndrome referred to endocrinology clinics.[7] Features that may prompt consideration of partial lipodystrophy in a patient with metabolic syndrome include early onset diabetes, fatty liver disease, requirement of excessive doses of insulin (>200 units/day), and persistently elevated triglycerides despite optimized lifestyle and therapeutic interventions.[1]

Our case with FPLD2 demonstrated manifestations of both lipodystrophic habitus and metabolic derangements associated with metabolic syndrome, namely, diabetes mellitus, PCOS, hypertriglyceridemia, and hepatic steatosis, all of which are known to manifest in FPLD2 patients.[8] On DNA sequencing, the patient was found to have a rare heterozygous mutation, p.R545H (c.1634 G > A), in the *LMNA* sequence. This mutation has been previously reported in a data set associated with heart failure, although detailed phenotypic information is lacking.[9] Furthermore, there is no clinical information elsewhere in the literature about the phenotype associated with this mutation. *LMNA* encodes homodimeric coiled-coil proteins lamins A and C, which are integral components of the nuclear lamina.[10,11] Lipoatrophy associated with FPLD2 is most likely due to disruption of nuclear lamina resulting in cell death or to disruption of the interaction between lamins and transcription factors such as SREBP1.[12]

Patients with a mutation in exon 11 of the *LMNA* gene have a phenotypically atypical and less severe form of lipodystrophy when compared with missense mutations in exon 8 that impact both lamin A and C.[13] However, most missense mutations have been reported to reside within exons 11 and 12 at the 3'-end of the gene, which are specific for the lamin A isoform.[14] On the other hand, effected patients with mutations in exon 1 (p.R28 W and p.R62 G)