Case Report
Familial partial lipodystrophy with gene mutation in both LMNA and PPARG: report of a case and review of literature

Guiming Zhou¹, Yang Wang², Mei Xu³

Departments of ¹Ultrasound, ²Radiology, ³Paediatrics, Tianjin Medical University General Hospital, Tianjin 300052, China

Received December 9, 2015; Accepted April 26, 2016; Epub December 1, 2016; Published December 15, 2016

Abstract: Lipodystrophies are a group of rare diseases characterized by the loss of adipose tissue. Familial partial lipodystrophy (FPLD) is often associated with fat accumulation in nonatrophic depots. FPLD is linked to a single mutation in the lamin A/C (LMNA) or peroxisome proliferator-activated receptorγ (PPARG). We report an FPLD case with a gene mutation in both LMNA and PPARG. Analysis of the coding region of LMNA revealed a heterozygous C-to-T mutation at nucleotide 1698 in exon 15. Similarly, analysis of the coding region of PPARG revealed a heterozygous C-to-T mutation at nucleotide 1431 in exon 8. The patient presents a loss of subcutaneous fat in the face and extremities, but increased subcutaneous fat in the neck, shoulder, and vulva. The patient also presents severe aortic and main pulmonary artery stenosis. Conclusion: An interaction between the two mutations may worsen the clinical symptoms, and/or lead to atypical clinical symptoms.

Keywords: Lipodystrophies, familial partial lipodystrophy, LMNA mutation, PPARG mutation

Introduction
Lipodystrophies are a group of rare diseases characterized by the loss of adipose tissue, which can be classified into localized (partial lipodystrophy) or generalized by the extent of fat loss [1]. They are classed as genetic or acquired according to the etiology [2, 3]. Familial partial lipodystrophy (FPLD) is often associated with fat accumulation in nonatrophic depots. Affected people show complications such as diabetes mellitus, insulin resistance, hypertriglycerideremia, acanthosis nigricans, hepatic steatosis, cardiac hypertrophy and hypertension. FPLD is broadly subdivided into three types: FPLD1 (Kobberling type), FPLD2 (Dunnigan type) and FPLD3 [1]. FPLD2 is linked to a mutation in the lamin A/C gene (LMNA), which encodes the A-type lamins (lamin A and lamin C). Mutations in LMNA cause several diseases called “laminopathies” including progeroid syndrome and lipodystrophies with metabolic alterations and cardiovascular complications [4, 5]. FPLD3 is associated with a mutation in the PPARG encoding the peroxisome proliferator-activated receptorγ (PPARγ). PPARγ plays an important role in adipose tissue metabolism [6]. Patients with FPLD3 may exhibit disorders of metabolism, such as insulin resistance, dyslipidemia, and hypertension. Mutations in PPARG are also associated with several cardiovascular diseases [7].

FPLD appears to always result from a single gene mutation such as LMNA mutation in FPLD2 or PPARG mutation in FPLD3. We were unable to find any published description of a double or multi-gene mutation in a single type of FPLD. Here, we report a case of FPLD with a mutation in both LMNA and PPARG.

Case report
A 13-year-old female Chinese patient was referred to Tianjin Medical University General Hospital with impaired glucose metabolism. She had a history of voracious appetite, polydipsia, and polyuria over 2 months, with more severe symptoms after she caught a cold 1 week previously. She was born by cesarean delivery after...
a full-term pregnancy. At 2 years of age, she was diagnosed with rickets. Over the third year of life, she developed unusual facial features with a triangular chin but abnormal fat accumulation on the neck and shoulders. At 5 years of age, she underwent surgical excision of the excess fat. She also had fat accumulation on the vulva since 3 months of age.

Biochemical evaluations showed hyperglycemia and dyslipidemia. The fasting blood glucose was raised at 20.9 mmol/L (normal upper limit = 6.4 mmol/L) and 120 min blood glucose after a meal was raised at 26.7 mmol/L. Glycosylated hemoglobin was 5.5%. Triglycerides were raised at 13 mmol/L (normal upper limit = 1.7 mmol/L). Glucose in the urine was ‘three plus’. Renal function and FT3, FT4, TSH, FSH,
and LH levels were normal. The patient had a normal 46XX karyotype.

Two-dimensionalechocardiographic examination showed homogeneous and mild left ventricular hypertrophy. Left-ventricle systolic function was normal, with an ejection fraction of 67%. The mitral valve was mildly thickened with the anterior leaflet mildly prolapsing to the left atrium during systole. The main pulmonary artery diameter was 14 mm (Figure 1A), the ascending aorta diameter 11 mm, aortic arch diameter 10 mm, and thoracic aorta diameter 7.5 mm (Figure 1B). The posterior pericardium showed 2-4 mm of fluid-filled dark space. Doppler echocardiography showed that the mitral valve had mild-to-moderate regurgitation. The peak flow velocity of the thoracic aorta was 3.03 m/s (Figure 1C). Pulmonary valve systolic velocity was 1.38 m/s and maximum systolic pressure of the pulmonary artery was 29 mmHg. Abdominal ultrasound revealed that the abdominal aorta diameter was 7.4 mm (Figure 1D).

We performed molecular analysis of multiple genes: LMNA, PPARG, LMNB2, AGPAT2, BSCL2, and AKT2. We found that the patient carried an LMNA mutation in exon 15 and a PPARG mutation in exon 8 (Table 1). Clinical diagnosis of FPLD was confirmed by the identification of mutations in LMNA and PPARG.

Discussion

FPLD, first described in the 1970s [8, 9], shows autosomal dominant inheritance. FPLD is characterized by fat loss in the extremities, followed by fat hypertrophy at truncal sites during childhood, puberty or early adulthood [2, 3, 10]. FPLD can be subdivided into three types according to the type of genetic mutation. FPLD1 (Kobberling type) is rarely reported in the literature [11]. FPLD2 results from mutations in the LMNA gene; mutations in this gene cause several diseases including progeroid syndrome, lipodystrophies (insulin resistance, hypertriglyceridemia, depressed high-density lipoprotein cholesterol, mild acanthosis nigricans, hirsutism, polycystic ovarian syndrome, and menstrual irregularities) and cardiovascular complications [4, 5]. FPLD3 results from mutations in the PPARG gene, which encodes the adipose transcription factor PPARγ. Mutations in PPARγ lead to less severe forms of lipodystrophy than do mutations in LMNA, affecting the extremities and the buttocks, but more severe hypertension and other metabolic abnormalities [12].

Our case carried a novel double genetic mutation: heterozygous c.1698C>T variant in exon 15 of LMNA and a heterozygous c.1431C>T variant in exon 8 of PPARG (Figure 2). Different mutations in LMNA can affect the resulting phenotype. Heterozygous p.R842W (c.1444 C>T) variant in exon 8 is the most common mutation in LMNA [13]. Patricia et al. reported that some patients with FPLD2 harbored heterozygous p.R482Q (c.1445G>A) or p.N466D (c.1396A>G) mutation in exon 8, or were homozygous for a p.R584H (c.1751G>A) mutation in exon 11. In addition, a novel variant p.R582C (c.1744C>T) in exon 11 and a p.R349W (c.1045>T) variant in exon 6 have been...
FPLD with gene mutation in both LMNA and PPARG

described [14, 15]. The heterozygous c.1698 C>T mutation in exon 15 in our case is the first description of this mutation in FPLD.

The mutational spectrum of PPARG and the resulting phenotypes are diverse. Visser et al. found a heterozygous p.R194W and p.Y151C mutation in FPLD patients with diabetes [16]. Angelik et al. studied a novel change at nucleotide 1270 in PPARG exon 5 (p.D424N) [12]. A heterozygous p.R425C (c.1273C>T) mutation has also been reported [17]. In our case, the patient harbored a heterozygous C-to-T change at nucleotide 1431 in exon 8. Anil et al. also reported a c.1431C>T change, but the mutation was in exon 6, not in exon 8 [17].

We assume that the double genetic mutation in our patient caused a unique combination of symptoms and physical signs. Our patient presented with an unusual fat distribution: fat loss on her face but fat accumulation on her neck, shoulders, and vulva. This fat distribution has not been described in previous studies. FPLD patients with LMNA mutation always show typical lipatrophy of the limbs and trunk, and excess subcutaneous fat in the chin and supraclavicular area. However, patients with PPARG mutation display loss of subcutaneous fat in the face and neck. It is reported that an increase in subcutaneous fat on the abdomen is the best way to discriminate patients with FPLD due to PPARG or LMNA mutation [12]. However, our patient did not show abdominal accumulation of subcutaneous fat. In our case, the patient had normal blood pressure, although hypertension has been reported to be associated with PPARG and LMNA mutations. Interestingly, our case presented a rare aortic and main pulmonary artery stenosis. Although cardiomegaly, left ventricular hypertrophy, valvular disease and atherosclerosis have been reported in lipodystrophies [18-21], only Araújo-Vilar et al. have reported an FPLD patient with aortic stenosis, left ventricular hypertrophy, and severe calcification of the aorta extending to a mitral annulus [22]; the aortic stenosis was not as severe as the aortic and main pulmonary artery stenosis in our case. In addition, our patient presented thick, black, curly hair, mild acanthosis nigricans, hyperglycemia and hypertriglyceridemia, which have not been reported in previous research related to either PPARG or LMNA mutations.

The mechanisms by which the double genetic mutation leads to the symptoms and physical signs in this patient are still unclear. Lamin A and lamin C polymerize with the B-type lamins to form a constituent of the nuclear lamina that exists in most differentiated somatic cells. The LMNA gene plays a role in DNA replication, chromatin anchoring, and spatial orientation in the nuclear pore complex, and forms a complex with nuclear envelope proteins [1, 15]. Meanwhile, PPARγ, which induces nuclear transcription factors, plays an important role in the regulation of adipose tissue and glucose metabolism [23-25]. An interaction between the mutations in LMNA and PPARG may worsen the clinical symptoms, and/or result in atypical clinical symptoms. This phenotype needs further investigation.

Acknowledgements

This work was financially supported by grants from The Found of the Health Bureau of Tianjin (2011KZ111) and the National Key Clinical Specialty Project. We wish to thank all our colleagues in Tianjin Medical University General Hospital. The authors declare no conflicts of interest.

Disclosure of conflict of interest

None.

Address correspondence to: Mei Xu, Department of Paediatrics, Tianjin Medical University General Hospital, 154 Anshan Road, Tianjin 300052, China. Tel: +86-22-60814075; E-mail: tjxumei@126.com

References


