European Journal of Medical Genetics 59 (2016) 320–324

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Spectrum of clinical manifestations in two young Turkish patients with congenital generalized lipodystrophy type 4

Gulcin Akinci [a, *], Haluk Topaloglu [b], Baris Akinci [c], Huseyin Onay [d], Cem Karadeniz [e], Yakup Ergul [f], Tevfik Demir [c], Emin Evren Ozcan [g], Canan Altay [h], Tahir Atik [i], Abhimanyu Garg [j]

[a] Division of Pediatric Neurology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey
[b] Division of Pediatric Neurology, Department of Pediatrics, Hacettepe University, Ankara, Turkey
[c] Division of Endocrinology and Metabolism, Department of Internal Medicine, Dokuz Eylul University, Izmir, Turkey
[d] Department of Medical Genetics, Ege University, Izmir, Turkey
[e] Division of Pediatric Cardiology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey
[f] Department of Pediatric Cardiology, Istanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center and Research Hospital, Istanbul, Turkey
[g] Department of Cardiology, Dokuz Eylul University, Izmir, Turkey
[h] Department of Radiology, Dokuz Eylul University, Izmir, Turkey
[i] Division of Pediatric Genetics, Department of Pediatrics, Ege University, Izmir, Turkey
[j] Division of Nutrition and Metabolic Diseases, Center for Human Nutrition, Department of Internal Medicine, UT Southwestern Medical Center at Dallas, Dallas, TX, USA

ARTICLE INFO

Article history:
Received 24 February 2016
Received in revised form
19 April 2016
Accepted 4 May 2016
Available online 7 May 2016

Keywords:
Arrhythmia
Lipodystrophy
Insulin resistance
Myopathy
PTRF

ABSTRACT

Congenital generalized lipodystrophy type 4 is an extremely rare autosomal recessive disorder. We report our clinical experience on two unrelated Turkish patients with congenital generalized lipodystrophy type 4. A 13-year-old girl (patient-1) presented with generalized lipodystrophy and myopathy. Further tests revealed ventricular and supraventricular arrhythmias, gastrointestinal dysmotility, atlantoaxial instability, lumbosacral scoliosis, and metabolic abnormalities associated with insulin resistance. A 16-year-old girl (patient-2) with congenital generalized lipodystrophy type 4 was previously reported. Here, we report on her long term clinical follow-up. She received several course of anti-arrhythmic treatments for catecholaminergic polymorphic ventricular tachycardia and rapid atrial fibrillation. An implantable cardioverter defibrillator was also placed. A homozygous *PTRF* mutation, c.259C > T (p.Gln87*), was identified in patient-1. Congenital generalized lipodystrophy type 4 was caused by homozygous *PTRF* c.481-482insGTGA (p.Lys161Serfs*41) mutation in patient-2. Our data indicate that patients with congenital generalized lipodystrophy type 4 should be meticulously evaluated for cardiac, neuromuscular, gastrointestinal and skeletal diseases, as well as metabolic abnormalities associated with insulin resistance.

1. Introduction

Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disorder characterized by near total absence of adipose tissue at birth or shortly thereafter (Garg, 2011). Until now, mutations in four different genes have been linked to CGL. Mutations in 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*) (Agarwal et al., 2002), Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*) (Magre et al., 2001) and caveolin 1 (*CAV1*) (Kim et al., 2008) genes were identified in CGL type 1, type 2 and type 3, respectively. Simha et al. (Simha et al., 2008) reported a novel subtype of CGL associated with muscular weakness and cervical spine instability in two Mexican American siblings. Afterwards, mutations in the polymerase I and transcript release factor (*PTRF*) gene, encoding a caveolar-associated protein that is essential for formation of caveolae and proper localization, were reported by Hayashi et al. (Hayashi et al., 2009), resulting in a similar phenotype which was called as CGL type 4.

In addition to generalized lipodystrophy and myopathy, CGL type 4 presents gastrointestinal dysmotility, skeletal abnormalities,

* Corresponding author.
E-mail address: akinci.gulcin@gmail.com (G. Akinci).

http://dx.doi.org/10.1016/j.ejmg.2016.05.001
1769-7212/

and cardiac arrhythmias (Simha et al., 2008; Hayashi et al., 2009; Shastry et al., 2010). Rajab et al. (Rajab et al., 2010) reported mutations in *PTRF* in eight families with CGL and myopathy of whom five members had died from sudden cardiac death during their teenage years. Electrocardiography (ECG) studies from these patients revealed long-QT interval, bradycardia, as well as supraventricular and ventricular tachycardias. Our previous report suggested that CGL type 4 was associated with catecholaminergic polymorphic ventricular tachycardia (CPVT) (Shastry et al., 2010). CPVT is characterized by stress induced ventricular tachycardia, and has a mortality rate of 30% in symptomatic patients when not treated (Kontula et al., 2005).

Here, we report our clinical experience on two young Turkish girls with CGL type 4. Both affected subjects underwent genetic, laboratory and radiological studies. We also report long-term clinical follow-up of one patient regarding metabolic abnormalities and persistent cardiac arrhythmias.

2. Clinical report

2.1. Patient-1

This 13-year-old Turkish girl was admitted with complaints of difficulty on walking and atypical appearance. She was born after full-term gestation via spontaneous vaginal delivery with a birth weight of 3600 g. Parents were reportedly not consanguineous; however they were from the same Anatolian town with a population of around 7000 people. Her parents first noticed increased musculature when she was 9 months of age. She was discovered to have elevated CK levels when she was 15 months old. Developmental milestones were mildly delayed. She was able to hold her head up at 4 months. She was able to walk at 18 months. There was no family history for lipodystrophy or muscular dystrophy.

Physical examination showed generalized lack of subcutaneous fat, acromegaloid appearance, large tongue, umbilical prominence, muscular hypertrophy and prominent veins in the limbs. Weight and height were at 25th percentiles, and head circumference was normal for age. “Mounding” and Percussion Induced Rapid Contractions (PIRCs) could be elicited in response to taps at the deltoid, biceps and forearm muscles with reflex hammer (Fig. 1a). She exhibited good strength of 5/5 in extremities. Deep tendon reflexes were normal. No acanthosis nigricans was visible.

Blood tests showed an elevated CK level of 1496 IU/L (normal range: 29–168 IU/L) and normal levels of AST (33 IU/L, normal range: <50 IU/L) and ALT (47 IU/L, normal range: <50 IU/L). Her fasting serum triglycerides were 321 mg/dL (normal range: 40–150 mg/dL), HDL cholesterol: 22 mg/dL (normal range: >50 mg/dL), and LDL cholesterol: 37 mg/dL (normal range: 30–160 mg/dL). Her fasting glucose level was 107 mg/dL (normal range: 70–100 mg/dL). Fasting C-peptide level was 4.34 ng/mL (normal range: 1.1–4.4 ng/mL), and insulin level was 8.64 μIU/mL (normal range: <25 μIU/mL). HOMA score was 2.29. Serum leptin level was undetectable (<0.1 ng/mL; normal range: 3.4–13 ng/mL).

Generalized lipodystrophy was demonstrated by whole body magnetic resonance imaging (MRI) (Fig. 1b). Genotyping revealed a homozygous *PTRF* null mutation, c.259C > T in exon 1 (p.Gln87*). Her parents and a sibling were carriers for the heterozygous mutation c.259C > T (Fig. 1c).

Atlantoaxial instability was detected on cervical spine X-ray (Fig. 1d). Gastrointestinal dysmotility was evident on barium radiographs. X-rays of the thoraco-lumbar spine revealed moderate lumbosacral scoliosis (Fig. 1e). Resting ECG was normal with a normal QT interval. Echocardiogram did not show any structural abnormalities. Holter monitoring revealed several runs of asymptomatic non-sustained ventricular tachycardia and supraventricular tachycardia episodes consistent with atrial tachycardia (Fig. 1f). During the treadmill stress test (Fig. 1g), non-sustained ventricular tachycardia developed at 6th minute of the exercise on Bruce Protocol at stage 3 with a sinus heart rate of approximately 140 beats per minute. Afterwards, atrial tachycardia developed at 7th minute of the exercise on Bruce Protocol at stage 3. She was commenced on propranolol (4 mg/kg/day).

2.2. Patient-2

This 11-year-old Turkish girl was first referred to our clinic because of scoliosis and atypical appearance and has been reported previously (Shastry et al., 2010). Blood tests revealed a CK level of 2337 IU/L (normal range: 29–168 IU/L). Serum leptin level was 0.58 ng/mL (normal range: 3.4–13 ng/mL). Near total lack of fat was demonstrated by whole body MRI (Fig. 2a). She was diagnosed with CGL type 4 caused by a homozygous insertion, c.481-482insGTGA in exon 2 of *PTRF* which was predicted to result in a frame shift making an abnormal protein p.Lys161Serfs*41. Her parents and a sibling were carriers for the heterozygous mutation c.481–482insGTGA (Fig. 2b).

Atlantoaxial instability was evident (Fig. 2c). She had tight heel cords due to shortening of the Achilles tendon. Scoliosis was severe on radiological studies (Fig. 2a and f). She underwent surgeries for scoliosis and shortening of the Achilles tendon during follow-up (at age 13). No arrhythmias or untoward events were reported and the patient recovered well from these surgeries. She had gastrointestinal dysmotility. Her triglyceride (109 mg/dL, normal range: 40–150 mg/dL) and LDL cholesterol (63 mg/dL, normal range: 30–160 mg/dL) levels were within the normal ranges; however HDL cholesterol level was low (23 mg/dL, normal range: >50 mg/dL). Thereafter, she developed mild hypertriglyceridemia at age 15. Her recent fasting glucose level was 106 mg/dL (normal range: 70–100 mg/dL), C-peptide level was 6.32 ng/mL (normal range: 1.1–4.4 ng/mL), and insulin level was 28.46 μIU/mL (normal range: <25 μIU/mL) with a HOMA score of 7.45.

At 12 years of age, she first complained of intermittent palpitations that initiated a cardiac evaluation. On ECG, there was no evidence of QT prolongation. Echocardiogram was normal. 24-h ECG monitoring revealed non-sustained episodes of VT and polymorphic VES beats (Fig. 2d). An exercise study was conducted which revealed several runs of asymptomatic bidirectional VT that strongly resembled CPVT. She was commenced on propranolol (4 mg/kg/day) which resulted in resolution of palpitations for 3 months. However, repeat Holter monitoring showed episodes of CPVT. The patient was switched to metoprolol, but CPVT episodes didn't resolve. The exercise stress test showed CPVT on stage 4 under the beta blocker therapy during her follow-up (Fig. 2e). ICD implantation was performed (Fig. 2f). During a follow up of 12 months on ICD, no device-related local complication was observed. Several short traces of CPVT were recorded, all of which converted to sinus rhythm spontaneously without any need of ICD shock. The records showed that she experienced several episodes of rapid atrial fibrillation. One of these episodes initiated ICD shocks which triggered a CPVT episode. She received 6 subsequent shocks of 34.6 J, which didn't resolve the arrhythmia each time. After the 6th shock, the device got exhausted and the arrhythmia terminated spontaneously (Fig. 2g). ICD set-up was reviewed and adjusted accordingly. Verapamil (6 mg/kg/day) and flecainide (100 mg/m^2/day) were added to her anti-arrhythmic treatment.

This case study was approved by the Dokuz Eylul University Ethics Review Panel. Both patients and parents provided written informed consent.