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Partial lipodystrophy of the limbs in a diabetes clinic setting

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ABSTRACT

Objective: Partial lipodystrophy of the limbs (PLL) is a newly described form of lipodystrophy that is characterized by symmetrical distal lipoatrophy of the limbs and insulin resistant diabetes.

Research design and methods: In this study, we prospectively screened our patients with type 2 diabetes for the presence of PLL phenotype. Metabolic parameters of PLL patients were compared to those with type 2 diabetes who applied to our diabetes clinic during the same period of time.

Results: Between Sep 2013 and Mar 2015, 2020 patients with type 2 diabetes were evaluated for the presence of PLL. PLL was confirmed in 16 patients. The prevalence of PLL was calculated as 0.79% in our diabetes clinic. The most common phenotypic presentations were loss of subcutaneous fat in the forearms, calves and thighs, and loss of fat in forearms and calves. Patients with PLL had poor metabolic control and marked insulin resistance compared to subjects with type 2 diabetes. Diabetes had been diagnosed at a younger age in patients with PLL. Patients with PLL also had more atherogenic lipid profiles.

Conclusions: Our data suggests that PLL is a relatively common form of lipodystrophy in diabetes clinics, which is associated with poor metabolic control and marked insulin resistance. The recognition of PLL in patients with type 2 diabetes can help better clinical management by alerting the physician to these associated co-morbidities.

1. Introduction

Lipodystrophies are a heterogeneous group of disorders characterized by impaired adipose tissue distribution and metabolism [1]. Fat is near-totally absent in patients with generalized lipodystrophies, whilst the lack of fat is selective in patients partial lipodystrophies. Several genes have been identified for congenital generalized lipodystrophy (CGL) [2–6] and familial partial lipodystrophy (FPL) [7–10]. On the other hand,

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fat loss has no genetic basis in acquired generalized lipodystrophy (AGL) and acquired partial lipodystrophy (APL) [1].

Lipodystrophies are commonly associated with metabolic abnormalities. Poorly controlled diabetes, severe hypertriglyceridemia and hepatic steatosis may be observed in patients with lipodystrophy as a result of marked insulin resistance which is believed to be secondary to fat tissue dysfunction [11].

Recently, Strickland et al. [12] has described a novel form of lipodystrophy, partial lipodystrophy of the limbs (PLL), which is characterized by symmetrical distal lipodystrophy of the limbs and insulin resistant diabetes. Using hyperinsulinemic clamp studies, they showed that insulin resistance was more prominent in patients with PLL compared to patients with type 2 diabetes. When compared to other non-HIV related forms of lipodystrophy, which have very rarely been reported in the literature, the authors proposed that this novel lipodystrophy subtype would affect larger number of patients in the real life.

To determine the prevalence of PLL in a diabetes clinic, we prospectively screened our patients with type 2 diabetes for the presence of PLL phenotype. Whole body MRI was used to confirm the diagnosis. Metabolic parameters of PLL patients were compared to those with type diabetes who applied to our clinic during the same period of time.

2. Patients and methods

A total of 2020 patients with type 2 diabetes, who were admitted to our diabetes clinic between Sep 2013 and Mar 2015, were screened for PLL. The study was approved by the Dokuz Eylul University Ethics Review Panel.

PLL was clinically diagnosed based on characteristic fat loss pattern and supporting clinical findings associated with insulin resistance. Patients were considered as PLL if (I) lipodystrophy primarily involved the distal extremities (forearms or forearms plus calves), (II) the lipodystrophy pattern was symmetrical, and (III) the signs of insulin resistance were evident such as acanthosis nigricans, polycystic ovaries, insulin resistant diabetes, hypertriglyceridemia and hepatic steatosis.

Fat distribution was assessed by whole body magnetic resonance imaging (WB MRI). The WB MRI was performed by using a 1.5-T MR device (Gyroscan Intera, release 8.1; Philips Medical Systems, Best, the Netherlands) with a 6 multichannel body coil. MR images of all patients were interpreted by 2 radiologists (M.S. and C.A.) with consensus. After the MRI study, patients were excluded if (I) increased visceral or subcutaneous fat was observed, but no lipoatrophy can be visualized in the distal extremities, (II) the lipodystrophy pattern was not symmetrical, (III) there was some lipoatrophy on the extremities, but no distal involvement was observed, and (IV) there was gluteal or anterior thorax involvement.

Mutation analysis of the genes LMNA, LMNB2, PPARG, CAV1, PLIN1, AKT2, and CIDEC were carried out by direct automated DNA sequencing from the patients' genomic DNA based on the clinical features. PCR primers used in order to amplify the regions of interests could be sent upon request. Sequencing was performed with Miseq V2 chemistry on MiSeq instrument (Illumina California, USA). Analysis was performed with IGV software.

All patients underwent detailed physical examination, full biochemistry and urinalysis for protein content. In patients with PLL, fasting insulin, C-peptide, leptin and adiponectin levels were measured. Hepatic steatosis was evaluated by high resolution ultrasound (US), conventional MRI and MR spectroscopy (MRS). The US was obtained with convex transducers (frequency bandwidth 3–6 MHz). Conventional MRI and MRS were performed by using a 1.5-T MR device (Gyroscan Intera, release 8.1; Philips Medical Systems, Best, the Netherlands) with a phased-array coil. Glucose, HbA1c, triglyceride and cholesterol levels were measured by standardized methods with appropriate quality control and quality assurance procedures. Insulin levels were measured by a chemiluminescent method. Homeostasis model assessment (HOMA-IR) score was calculated as fasting serum insulin (μIU/mL) × fasting plasma glucose (mg/dL)/405. Fasting C-peptide levels were measured by a chemiluminescent immunoassay. Leptin and adiponectin levels were measured with enzyme-linked immunosorbant assay (ELISA) according to the manufacturer's instructions (Boster, Pleasanton, CA, USA; Leptin: EK0439, sensitivity: <8 pg/mL; Adiponectin: EK0595, sensitivity: <60 pg/mL).

Statistical analysis was performed using Statistical Package of Social Science (SPSS Inc, Chicago, IL, USA), version 15.0 for Windows. Data was expressed as median (25–75 percentiles). Mann Whitey-*U* test was used for comparison of scale parameters. Categorical variables were compared by the chi-square test. A *p*-value less than 0.05 was accepted as statistically significant.

3. Results

Of 2020 patients with type 2 diabetes, 22 patients were candidates for PLL after physical examination. PLL was confirmed in 16 patients when WB MRI procedures were completed. Other 6 patients were considered as false positive cases. The prevalence of PLL was calculated as 0.79% in our diabetes clinic. Table 1 shows clinical characteristics of 16 patients with PLL. The median age was 51 (25–75 percentiles: 48–59). The age range was 41–66 years. 14 patients (87.5%) were women. Patients reported a median age of starting fat loss of 39 years (25–75 percentiles: 31–46). The BMI ranged from 25 kg/m^2 to 45.1 kg/m^2. The lipodystrophy pattern was symmetrical in all patients and only the limbs were affected. Loss of subcutaneous fat in the forearms, calves and thighs (6 patients, Fig. 1) and forearms and calves (5 patients) were the most common presentations, with lipodystrophy involving calves in three patients and calves and thighs in two patients. Intra-abdominal fat was increased. Fat accumulation was noticed in the scapular/neck area. None of the PLL patients had any mutation on genes which has been shown to cause partial lipodystrophy.

The laboratory data of patients with PLL is presented in Table 2. Fourteen patients (87.5%) had poorly controlled diabetes (HbA1c > 7%). Nine patients (56.2%) were on insulin. The average insulin dose was 113 units/day. Eleven patients (68.7%) had hypertriglyceridemia, and 11 (68.7%) patients had