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Acquired partial lipodystrophy is associated with increased risk for developing metabolic abnormalities

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ARTICLE INFO

Article history:
Received 2 February 2015
Accepted 4 June 2015

Keywords:
APL
Diabetes
Hepatic steatosis
Hypertriglyceridemia
Insulin resistance

ABSTRACT

Objective. Acquired partial lipodystrophy (APL) is a rare disorder characterized by progressive selective fat loss. In previous studies, metabolic abnormalities were reported to be relatively rare in APL, whilst they were quite common in other types of lipodystrophy syndromes.

Methods. In this nationwide cohort study, we evaluated 21 Turkish patients with APL who were enrolled in a prospective follow-up protocol. Subjects were investigated for metabolic abnormalities. Fat distribution was assessed by whole body MRI. Hepatic steatosis was evaluated by ultrasound, MRI and MR spectroscopy. Patients with diabetes underwent a mix meal stimulated C-peptide/insulin test to investigate pancreatic beta cell functions. Leptin and adiponectin levels were measured.

Results. Fifteen individuals (71.4%) had at least one metabolic abnormality. Six patients (28.6%) had diabetes, 12 (57.1%) hypertrigylceridemia, 10 (47.6%) low HDL cholesterol, and 11 (52.4%) hepatic steatosis. Steatohepatitis was further confirmed in 2 patients with liver biopsy. Anti-GAD was negative in all APL patients with diabetes. APL patients with diabetes

Abbreviations: APL, Acquired partial lipodystrophy; CGL, Congenital generalized lipodystrophy; MPGN, Membranoproliferative glomerulonephritis; FPL, Familial partial lipodystrophy; TuLip, Turkish Lipodystrophy Study Group; WB MRI, Whole body magnetic resonance imaging; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel; HDL, High density lipoprotein; AHA, American Heart Association; LDL, Low density lipoprotein; ADA, American Diabetes Association; GAD, Glutamic acid decarboxylase; US, ultrasound; MRS, Magnetic resonance spectroscopy; NASH, Nonalcoholic steatohepatitis; HOMA-IR, Homeostasis model assessment; ELISA, Enzyme-linked immunosorbant assay; ESRD, End stage renal disease; ANA, Antinuclear antibodies; OGTT, Oral glucose tolerance test.

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http://dx.doi.org/10.1016/j.metabol.2015.06.004

had lower leptin and adiponectin levels compared to patients with type 2 diabetes and healthy controls. However, contrary to what we observed in patients with congenital generalized lipodystrophy (CGL), we did not detect consistently very low leptin levels in APL patients. The mix meal test suggested that APL patients with diabetes had a significant amount of functional pancreatic beta cells, and their diabetes was apparently associated with insulin resistance.

Conclusions. Our results show that APL is associated with increased risk for developing metabolic abnormalities. We suggest that close long-term follow-up is required to identify and manage metabolic abnormalities in APL.

1. Introduction

Lipodystrophy is a rare disorder affecting adipose tissue distribution and metabolism [1]. Patients with acquired lipodystrophies develop fat loss at some point during life. Acquired partial lipodystrophy (APL) is characterized with fat loss typically starting at childhood or early adulthood. It usually first affects the face, and then progresses to the neck, upper extremities, and trunk, sparing some fat on the lower extremities. APL has been associated with abnormalities of the alternative complement pathway that may cause membranoproliferative glomerulonephritis (MPGN) and subsequent renal failure [2].

Previous reports, mostly case studies, suggested that metabolic abnormalities were rare in patients with APL, although several reports mentioned that hepatic steatosis and lipid abnormalities could occur in the form of raised triglyceride and decreased HDL cholesterol [1,3,4]. It was thought that preserved fat in the lower part of the body might be protective for metabolic abnormalities. In a previous review, Misra et al. [3] reported that the prevalence rates of diabetes and impaired glucose tolerance were 6.7% and 8.9%, respectively, which were apparently not different from the prevalence of carbohydrate intolerance in the general population. On the other hand, metabolic abnormalities are quite common in patients with other types of lipodystrophy syndromes such as congenital generalized lipodystrophy (CGL) and familial partial lipodystrophy (FPL) [5,6]. Limited data in APL are mostly based on cross-sectional case studies [1,3,7]. In these reports, clinical characteristics of patients with APL were mainly described when the diagnosis was first made. However, it is not clear if metabolic abnormalities develop in the course of the disease. Therefore, we have hypothesized that metabolic abnormalities may be more prevalent in APL than previously reported. To test our hypothesis, we have evaluated our nationwide APL registry for metabolic abnormalities.

2. Materials and Methods

The Turkish Lipodystrophy Study Group (TuLip) is a national platform that is committed to improve our knowledge on lipodystrophy syndromes by bringing together physicians who are interested in lipodystrophy syndromes throughout the country. Our current registry includes 94 non-HIV associated lipodystrophy patients. Of those, 27 patients were classified as APL. This study included data from 21 patients with APL in whom metabolic abnormalities were thoroughly evaluated. Five patients were not included in the analysis due to lack of regular prospective follow-up for metabolic abnormalities. Another patient was excluded as he had been treated with multiple drugs such as high dose systemic steroids for systemic lupus erythematosus. The data were collected by the members of TuLip in several centers. According to the prospective follow-up protocol of TuLip, every patient had detailed physical examination, full biochemistry and urinalysis for protein content at the time of diagnosis for lipodystrophy, after which he/she had these tests on a regular basis every 3–6 months. The registry was first reviewed retrospectively. Then, patients were asked to come for a visit to re-measure their biochemistry and update their clinical findings at the time of data collection. Control groups consisted of age- and gender-matched subjects. The healthy control group included apparently healthy subjects who were selected from the hospital staff. Diabetes was excluded using 75 g OGTT. The diabetic groups included patients with type 1 and type 2 diabetes who were selected from subjects attending the Diabetes Clinic at Dokuz Eylul University during the period of the study. CGL patients were registered in the TuLip database. The selection of all controls was carried out by using random sampling procedure. The study was approved by the Dokuz Eylul University Ethics Review Panel (protocol 2014/28-35). Informed consent was obtained in all cases.

APL was clinically diagnosed based on the fat loss characteristically starting at the face, progressing downwards to the trunk and upper extremities. 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 with a 6 multichannel body coil (Gyroscan Intera, release 8.1; Philips Medical Systems, Best, the Netherlands). To monitor the progression of fat loss, pictures were taken at every visit, and patients were asked to bring serial pictures from the past demonstrating the fat loss. When needed, mutation analysis of the genes *LMNA*, *LMNB2*, *PPARG*, *AGPAT2*, *BSCL2*, *CAV1*, *PTRF*, *PLIN1*, *AKT2*, and *CIDEC* was carried out by direct automated DNA sequencing from the patients' genomic DNA to eliminate genetic lipodystrophies. Sequencing was performed with Miseq V2 chemistry on MiSeq instrument (Illumina California, USA). Analysis was performed with IGV software.

Blood was taken from the cannulated antecubital vein between 8:00 a.m. and 9:00 a.m. after 10-h overnight fasting. Glucose, HbA1c, triglyceride, and cholesterol levels were measured by standardized methods with appropriate quality