We report the case of a 49-year-old woman with long-standing type 2 diabetes (mean glycated hemoglobin about 10% [86 mmol/mol] over the past years) that was never sufficiently controlled, intolerance against multiple antidiabetic agents (metformin, pioglitazone, glucagon-like peptide-1 receptor agonists), enormous daily insulin requirements (>300 insulin units), and high C-peptide levels (3.15; normal range 0.78–1.89 ng/ml), indicating marked insulin resistance. Comorbidities included morbid obesity, significant hypertriglyceridemia, low levels of high-density lipoprotein, arterial hypertension, and hepatic steatosis.

The patient’s body measurements were as follows: body weight of 137 kg and a height of 164 cm (body mass index, 49.1 kg/m²), total body fat 40.3%. Upon clinical examination, the woman presented with suspicious absence of subcutaneous adipose tissue at the lower extremities and gluteal region, feigning muscular appearance. In contrast adipose tissue in the abdominal region and trunk was well developed and excess fat was observed in the face, chin, and neck, resembling cushingoid appearance, while striae rubrae, skin atrophy, or muscle weakness were not present (FIGURE 1A-1C).

The onset of the physical transformation occurred when the patient was 3 years old. Similar physical features and metabolic alterations were reported in her mother and grandmother. In contrast, all of her male first-­degree relatives were normal. Familial partial lipodystrophy such as type 2 FPLD (Dunnigan disease, LMNA gene), to date, no pathogenetic mutations have been identified. A strong predictor for Köbberling syndrome is the ratio of truncal fat weight to body weight (in kilograms) (FIGURE 1D-1E). Endocrine diseases such as endogenous hypercortisolism, polycystic ovary syndrome, or hypothyroidism had been ruled out. Genetic testing excluded defects in the LMNA gene, which is associated with type 2 familial partial lipodystrophy (FPLD), Dunnigan disease.

After considering the metabolic impairments and the clinical features which were also present in female family members, we suspected type 1 FPLD, Köbberling syndrome, to be present in this woman. Köbberling syndrome, is an autosomal dominant inherited orphan disease which is rarely diagnosed; however, higher incidence rates than are actually reported can be assumed. So far, these clinical features have only been observed in women. In contrast to other forms of FPLD such as type 2 FPLD (Dunnigan disease, LMNA gene) or type 3 FPLD (PPAR-y gene), to date, no pathogenetic mutations have been identified.

Familial partial lipodystrophy syndromes are rare diseases characterized by variable loss of adipose tissue and metabolic comorbidities occurring during childhood or adolescence. The discrimination between different FPLD syndromes is frequently challenging as they often demonstrate similar anthropometric, clinical, and metabolic characteristics. The patient presented in this image is characterized by a loss of adipose tissue in the lower extremity with remarkably well-defined muscles especially of the calves/gluteal region, mostly excessive amounts of subcutaneous abdominal and truncal fat, as well as edematous and round face, feigning cushingoid appearance.13 Because of the onset of fat transformation which occurred during childhood and the negative screening for type 2 FPLD, we suggest type 1 FPLD, Köbberling syndrome, to be present in this woman. Köbberling syndrome, is an autosomal dominant inherited orphan disease which is rarely diagnosed; however, higher incidence rates than are actually reported can be assumed. So far, these clinical features have only been observed in women. In contrast to other forms of FPLD such as type 2 FPLD (Dunnigan disease, LMNA gene) or type 3 FPLD (PPAR-y gene), to date, no pathogenetic mutations have been identified. A strong predictor for Köbberling syndrome is the ratio of truncal fat weight (in kilograms) to fat weight of the lower limbs which was almost 5 in this patient (cutoff value, 2.153)1 assessed by dual-energy X-ray absorptiometry. Most patients are affected by impairments in glucose and lipid metabolism as well as fatty liver disease, increasing their risk of cardiovascular disease.3 It is assumed that such patients should be thoroughly diagnosed and an early initiation of intensive treatment of related comorbidities is recommended. Evidence suggests that patients with type 1 FPLD might benefit from bariatric surgery in terms of metabolic abnormalities and on cosmetic grounds.3
A woman with Köbberling syndrome characterized by the lack of subcutaneous fat in the lower extremities and gluteal region, remarkable fat excess in the abdominal area, and cushingoid-like moon face. D, F, F, G – childhood pictures with already existing body features characteristic of type 1 FPLD: the patient at the age of 6 years (D), at the age of 8 years with her mother (E), at the age of 10 years with her father and brother (F), at the age of 14 years with her brother (G). The authors obtained informed consent from the patient.

REFERENCES


