A woman with familial partial lipodystrophy and the complications of her four pregnancies

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Abstract

We discuss a case of a woman ultimately diagnosed with familial partial lipodystrophy following her fourth pregnancy. In her previous pregnancies she had numerous complications thought to be related to diabetes including recurrent macrosomia and polyhydramnios. In her second pregnancy she underwent emergency caesarean section for fetal tachycardia at 34 weeks' gestation. Her baby was diagnosed with unexplained cerebral ischaemic injury and limb ischaemia requiring amputation. Postnatally she was diagnosed with type 2 diabetes mellitus with subsequent poor control. Very high insulin demands in this fourth pregnancy and an unusual phenotypic appearance in the patient and her mother raised suspicion of an underlying condition. Genetic studies confirmed the clinical diagnosis of familial partial lipodystrophy.

Keywords

Clinical genetics, diabetes, maternal-fetal medicine, reproductive endocrinology, high-risk pregnancy

Case

A 38-year-old Caucasian lady presented to the diabetic antenatal clinic in her fourth pregnancy. Her first pregnancy at age 26 was uncomplicated other than delivery of a macrosomic female infant (5186 g) at 39 weeks' gestation. A glucose tolerance test (GTT) at booking had demonstrated a 2-hour reading of 8.0 mmol/l but had not been repeated in later gestation. During her second pregnancy at age 31 she developed GDM from 12 weeks' gestation (2-hour reading on a 75 g GTT 11.5 mmol/l), and required insulin for glycaemic control. Maximum total daily insulin requirements just prior to delivery were 92 units. At 34 weeks' gestation, during a fetal medicine ultrasound scan, a fetal tachycardia was noted. She was delivered by emergency caesarean section the following day for a non-reassuring cardiotocograph characterised by a persistent fetal tachycardia. Her preterm male infant, weighing 3350 g, was transferred to a tertiary centre at two days of life with suspected hypoxic ischaemic encephalopathy and a dusky blue arm. Investigations confirmed a cerebral ischaemic injury as well as ischaemic injury of the left arm which later required amputation. He made a good recovery. No cause was found for these ischaemic events; thrombophilia screen was negative. The patient opted for a first trimester termination of her third pregnancy on the grounds of concern for fetal developmental abnormalities related to poor glycaemic control (HbA1c 8.8%) at the time of conception. At that time she was on a combination of long- and short-acting insulin (110 units daily).

In the index pregnancy, her booking HbA1c was 7.7%. She had difficulty achieving glycaemic control from early gestation and required over 250 units of insulin daily and maximal doses of metformin (2 g) from 12 weeks' gestation. On physical examination she was of BMI 26, with excessively muscular limbs, and absent subcutaneous fat in her extremities and trunk, with neck and face sparing. Her mother was of the same phenotypic appearance and had been diagnosed with diabetes. Suspicion of an underlying genetic insulin-resistant syndrome was raised. Genetic studies were performed.

Despite close monitoring and higher doses of insulin, diabetic pregnancy complications ensued from 26 weeks' gestation with polyhydramnios (amniotic fluid index (AFI) 23) and macrosomia (abdominal circumference (AC) 243 mm). By 28 weeks' gestation, with an AFI of 33 and AC of 286 mm, she was admitted in an attempt to regain diabetic control by use of an intravenous (IV) insulin infusion, or if unsuccessful, to arrange delivery. Surprisingly her IV insulin requirements were very minimal with an average of 1 unit/hour. After 2

days she was restarted on subcutaneous insulin therapy, altering her injection site to her limbs, which helped initially. When glycaemic control deteriorated the following week, glibenclamide 7.5 mg was prescribed in addition to 250 units insulin and metformin 2 g daily. Although this appeared to improve control, the polyhydramnios and accelerated abdominal girth velocity continued to worsen and the decision was made to deliver early by caesarean section at 33 weeks' gestation after administration of steroids for fetal lung maturation. In the week preceding delivery, the HbA1c was 5.6% and triglyceride level 3.1 mmol/l.

Absence of subcutaneous fat was a marked observation at entry through Pfannenstiel incision during caesarean section (Figure 1), which was otherwise uncomplicated. Her female infant weighed 3280 g at birth (>90th centile for gestational age) and she required neonatal admission for management of hypoglycaemia. Following delivery the patient achieved glycaemic control on pioglitazone and metformin. The outcome of the genetic studies reported after delivery confirmed familial partial lipodystrophy (FPLD) of the Dunnigan variety. Leptin treatment was recommended.

Discussion

FPLD is a rare autosomal dominant disorder characterised by a normal appearance at birth, with gradual loss of subcutaneous fat from the extremities during puberty, and accumulation of adipose tissue in the neck and face, often leading to confusion with Cushing's syndrome.¹ However, plasma corticosteroid metabolism is normal in FPLD.² On investigation patients will usually present with hypertriglyceridemia and low HDL cholesterol levels, and by age 20 will develop glucose intolerance or diabetes, due to severe insulin resistance (IR).¹ FPLD can be diagnosed clinically, but definitive diagnosis

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Figure 1. Absence of subcutaneous fat noted on caesarean section in the index pregnancy.

requires genetic studies to confirm mutations in the Lamin A/C (LMNA) gene.

Of interest in this case were the minimal insulin doses needed when insulin was administered intravenously. It thus appeared that the majority of IR in this patient was due to lack of absorption of insulin from her subcutaneous tissue.

Genetic assessment of this woman revealed the R482W (Arg(482)Trp) missense LMNA mutation, which is the most common LMNA mutation associated with FPLD. As suspected clinically, the patient was diagnosed with FPLD of the Dunnigan variety with the type 2 clinical phenotype. She also had the associating features of this syndrome, including hyperinsulinaemia, acanthosis nigricans, hypertriglyceridemia and diabetes.

Studies have established a link between FPLD and an increased propensity towards developing cardiac arrhythmias.³ It was postulated that in utero arrhythmias may have caused emboli to the brain and arm in the patient's second child. Genetic studies are ongoing in her son.

There are limited studies exploring pregnancy outcomes in women with LMNA-related partial lipodystrophy, but a recent case series demonstrated that affected women have a higher risk of GDM, PCOS, infertility, miscarriages, macrosomia, eclampsia and fetal death.⁴ Hence women with LMNA mutations require intensive surveillance in pregnancy to achieve successful outcomes.

In conclusion, it is important that secondary causes of metabolic abnormalities including diabetes are considered in cases characterised by unexplained severe macrosomia and/or severe IR, as diagnosis may not only affect subsequent pregnancies, the long-term health of the woman but also has implications for other family members.

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Ethical approval

Written patient consent for publication was obtained.

Guarantor

SS

Contributorship

SN wrote the first draft of the manuscript. KL and SS reviewed and edited the manuscript and approved the final version of the manuscript.

Conflict of interest

None declared.

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