Electronic supplementary material

Patient 1 The early clinical course of Patient 1, from a Yemeni family with five affected members, has been described [1]. In brief, she experienced severe recurrent hypoglycaemia in infancy leading to seizures, which were treated with diazoxide for 2 years. Extreme hyperinsulinaemia and dysmorphic features led to a diagnosis of 'leprechaunism' at the age of 3 years, although we would prefer to label the same clinical and biochemical constellation of features as Rabson–Mendenhall syndrome. Diabetes mellitus was diagnosed at 8 years old. At 19 years of age her dominant problem is cosmetically distressing hyperandrogenisation amenorrhoea. Her therapy is 250 U insulin, 2,500 mg metformin, 15 mg pioglitazone and 100 mg cyproterone acetate daily. On examination she had a body mass index of 22.6 kg/m^2, mild virilisation, severe acanthosis nigricans, thickened skin and large hands and feet.

Patient 2 Little clinical information is available about the early history of Patient 2, the child of non consanguineous Somali parents. She is said to have had acanthosis nigricans before the age of 1 year, and by the time of formal evaluation at 9 years old, she had severe acanthosis nigricans, oligomenhorroea and polycystic ovaries, and extremely insulin resistant diabetes, with a fasting blood glucose of 2.7 mmol/l and fasting insulin of 1,040 pmol/l. Colonoscopy, undertaken to investigate gastrointestinal symptoms eventually attributed to coeliac disease, showed florid colonic polyposis, although multiple biopsies revealed a normal histological appearance. Since then her glycaemic control has been chronically poor despite treatment with up to 2,000 U insulin/day as well as metformin and rosiglitazone. At the age of 22 she has yet to suffer any microvascular complications of chronic hyperglycaemia and, despite chronic mild ketonaemia, has suffered no episodes of diabetic ketoacidosis. She has five siblings who are said to be unaffected, though none were available for study.

Patient 3 is the only one of eight siblings from a Somali family who is known to be affected by severe insulin resistance, although no other family members were available for biochemical or genetic study. She had poor growth throughout childhood and presented with diabetes mellitus at 7 years old, with poor subsequent glycaemic control despite high doses of insulin. After transfer to our care aged 16 years, episodes of mild hypoglycaemia were documented on three out of seven clinic visits during the first 18 months, whilst receiving 6 U/kg/day of soluble insulin, one episode requiring admission to hospital. When referred at aged 16 years, her height SDS was −5.03 and she was in early puberty. Her final adult height is 135.9 cm.

Patient 4 is the only one of five siblings born to consanguineous Somali parents known to be affected by severe insulin resistance. She was born at term with a birthweight of 3.0 kg, and initially both her length and weight followed the 97th centile. However, by 8 months old she had declined to the 10th centile for weight and the 50th for length, had developed thickened, darkened skin in her flexures, and had diffuse hypertrichosis. Over subsequent years she developed recurrent ear and tonsillar infections as well as premature eruption of her

secondary dentition and dental malocclusion. During investigation of a refractory dermatophyte infection at 5.5 years old she was formally evaluated for insulin resistance, and was found to have plasma insulin levels consistently between 1,000 and 2,000 pmol/l, with attendant postprandial hyperglycaemia, and treatment with insulin was commenced. Rapid dose increases were required to a maximum of 35 U/kg/day. On assessment at 9.9 years old, weight, height and body mass index were all on the 50th centile. There was severe and diffuse acanthosis nigricans, dental crowding and malocclusion, but examination was otherwise normal. Imaging revealed bilateral nephromegaly with calculi and ovaries with multiple follicles.

Patient 5 was born at 41 weeks gestation with a birthweight of 2.18 kg (−3.9 standard deviation score [SDS]) and a length of 45 cm (−3.5 SDS) to a father of Somali origin and a Europid French mother. He was dysmorphic with virilisation, and profound hypoglycaemia was noted at 1 day of age. He also showed evidence of postprandial hyperglycaemia. Plasma insulin concentrations were grossly elevated, with low IGF1 and IGFBP3 concentrations. A diagnosis of Donohue syndrome was made, and he was commenced on recombinant IGF1/IGFBP3 therapy, leading to an improvement in fasting tolerance from 1.75 to 5 h. At the age of 5.8 years, his height was 97.7 cm (−3.1 SDS) with a weight of 14.7 kg (−2 SDS). He has nephromegaly with nephrocalcinosis and marked acanthosis nigricans.

Reference

[1] al-Gazali LI, Khalil M, Devadas K (1993) A syndrome of insulin resistance resembling leprechaunism in five sibs of consanguineous parents. J Med Genet 30: 470–475