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Clinical report

A novel homozygous missense mutation in the insulin receptor gene results in an atypical presentation of Rabson-Mendenhall syndrome

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ABSTRACT

Leprechaunism (Donohue syndrome) and Rabson-Mendenhall syndrome are caused by mutations in the insulin receptor gene and are associated with extreme insulin resistance. Clinically these syndromes appear to represent points on a continuum of severity of receptor dysfunction, rather than completely distinct syndromes.

We investigated a Libyan infant with growth retardation, facial dysmorphism (elfin-like features), acanthosis nigricans and hirsutism. Fasting hypoglycaemia and postprandial hyperglycaemia with persistent hyperinsulinemia were found. A novel homozygous missense mutation was found in exon 2, resulting in a substitution of a glycine-132 for a serine in the INSR α-subunit (c.394G > A; p.Gly132Ser). At age ten, he developed diabetes mellitus. At age eleven, patient is still alive with mental retardation and severe growth retardation.

1. Introduction

Donohue syndrome or leprechaunism (OMIM: 246200) and Rabson-Mendenhall syndrome (OMIM: 262190) are two rare autosomal recessive conditions caused by mutations in the *INSR* gene. Leprechaunism or Donohue syndrome (DS) is the most severe form of inherited insulin resistance syndromes. It is characterized by intrauterine growth retardation, dysmorphic features, acanthosis nigricans, hirsutism and severe insulin resistance with early demise within the first year of age (Longo et al., 2002; Park et al., 2005). Rabson-Mendenhall syndrome (RMS) is somewhat less severe, with progressive hyperglycemia and eventual development of refractory ketoacidosis, together with somatic anomalies and survival up to the third decade.

In this study, we describe a previously unreported patient with a clinical phenotype resembling leprechaunism with typical dysmorphic features but with a sustained survival and a mild clinical outcome.

1.1. Clinical report

The patient M. was the first male infant born at term to a consanguineous Libyan parents, with a birth weight of 2150 g (below the third centile). During the neonatal period, he had a prolonged episode of hypoglycaemia and a haemolytic anaemia needing blood transfusion support. At the age of nine months, he was referred for suspicion of lysosomal storage disease. He had growth delay with a weight of 5500 g (below the third centile), a height of 62 cm (below the third centile), and a head circumference of 42 cm (−2,5 standard deviations). Dysmorphic features noted were an elfin-like facies, prominent eyes, upturned nostrils, thick lips, large and low-set ears. Other features included hirsutism as well as loose dry skin lying in folds (Fig. 1). Acanthosis nigricans was present in axillae, neck and periorbital region (Fig. 2) with gynecomastia, enlarged external genitalia and umbilical hernia. A psychomotor retardation completed the clinical pattern. Normal investigations included liver function test, renal function test, Adrenocorticotrophic hormone, thyroxine, *Thyroid-stimulating hormone,* 17-hydroxyprogesterone, renal ultrasound and karyotype. Blood tests looking at glucose and insulin profile during a fasting period showed a fasting hypoglycaemia with elevated levels of circulating insulin (6140μU/ml); post prandial hyperglycaemia was

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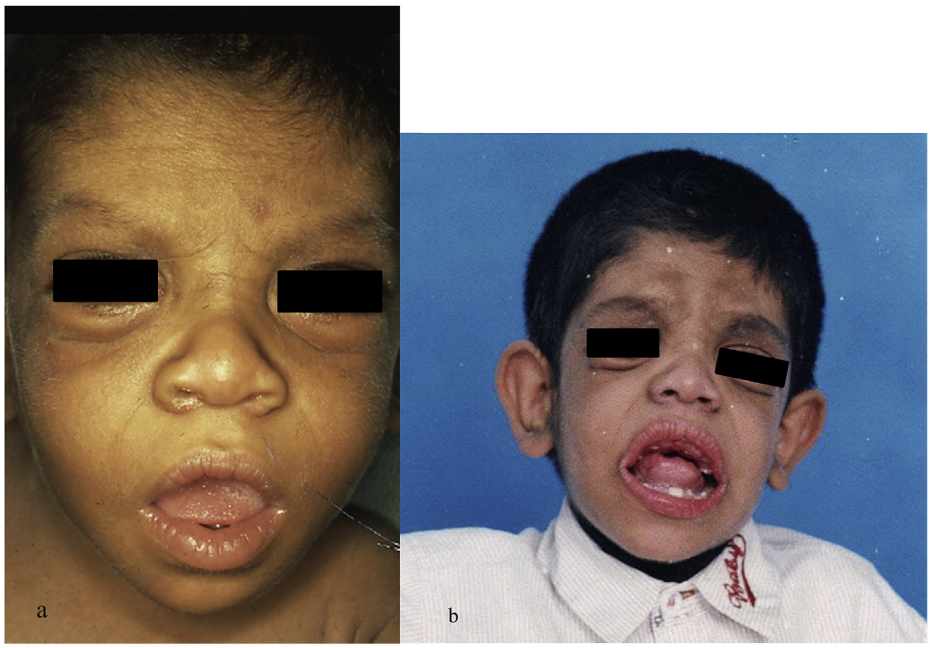

Fig. 1. Dysmorphic features(at ages 9 months) and 5 years. We note dysplastic teeth and gingival hypertrophy on Fig. 1b.

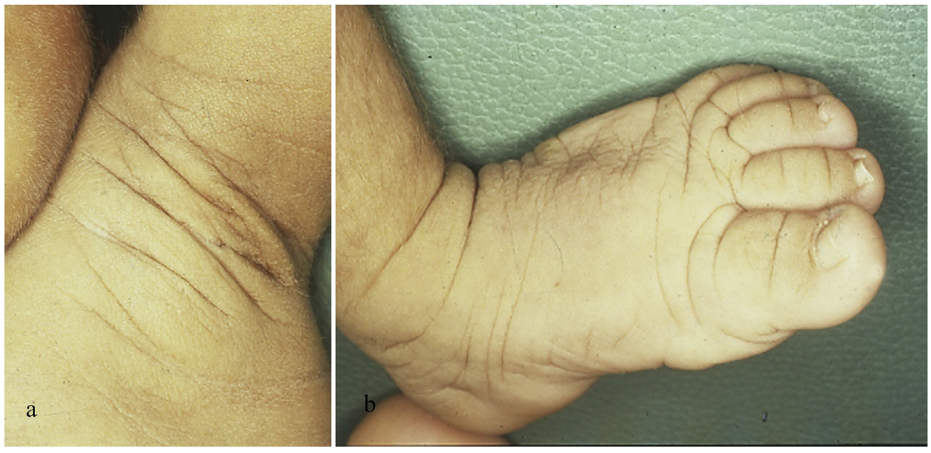

Fig. 2. Acanthosis nigricans with flat skin and hypertrichosis.

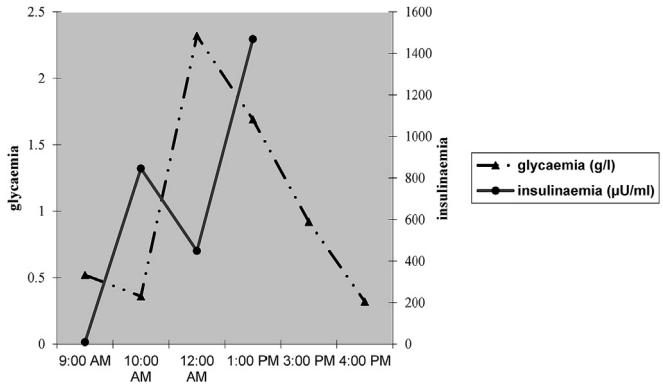

Fig. 3. Insulinaemia–glycaemia cycle.

noted despite elevated insulin levels (Fig. 3). These clinical and biochemical findings are in keeping with a diagnosis of leprechaunism

The DNA sequencing of the *INSR* gene using Polymerase Chain Reaction (PCR) amplification indicated that the patient had a homozygous missense mutation that consists in a G > A substitution at base pair 532 in the exon 2 which results in a substitution of a glycine-132 for a serine (c.394G > A; p.Gly132Ser) in the INSR α-subunit. Both parents were heterozygous for this mutation. As it was a novel mutation, we submitted it on CLINVAR (accession number SCV000245566**).** We could not investigate the biochemical effect of this mutation, but the comparison of the Homo sapiens insulin receptor mRNA to that of other species shows that the glycine 132 is a conserved residue (Fig. 4). We tested the effect of this mutation using two of the most known protein folding prediction software program, Polyphen and SIFT. This mutation is predicted to be probably damaging.

After discharge, the proband was followed up locally for a few months and then was followed up in Libya. At age five he was noted to have abnormal teeth with gingival hypertrophy (Fig. 1b) with