Case Report:

Rabson Mendenhall Syndrome; a case report

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Abstract

A 13 year old girl presented with severe hyperglycemia. In spite of taking large doses of insulin, her sugars were uncontrolled. She had severe acanthosis nigricans, a feature of severe insulin resistance. There was associated growth retardation, dental dysplasia, excessive body hair and clitoromegaly. Genetic studies revealed a point mutation in Insulin receptor gene (INSR) confirming the diagnosis of Rabson Mendenhall Syndrome. This mutation was also detected in both her parents in heterozygous condition. She responded to insulin sensitizers administered along with high doses of insulin.

Key words: Diabetes, hirsuitism, insulin resistance, INSR gene, Rabson Mendenhall syndrome, mutations.

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Introduction

Rabson Mendenhall syndrome is a rare genetic disorder characterized by severe insulin resistance. Homozygous mutations in Insulin receptor gene (INSR) are responsible for this syndrome (1).

The human insulin receptor is a heterotetramer composed of two extracellular alpha subunits that bind insulin and two beta subunits that span the plasma membrane and have an intracellular tyrosine kinase domain (2). Mutations in the INSR gene cause inherited insulin-resistance syndromes (i.e. abnormal glucose homeostasis, acanthosis nigricans and ovarian hyperandrogenism) which range from mild to severe (3).

Case presentation

A 13 year old girl of Asian Indian origin presented to us with poorly controlled diabetes of 7 years duration. She was on large doses of insulin but her HbA1c was grossly elevated at 12.5%.

She was born as the second child of first degree consanguineous parents. She was full term at birth and was delivered by lower segment cesarean section (LSCS) with a birth weight of 2.0 kg. She was developmentally normal and did well at school. She had an elder sister, who had similar clinical features and died at the age of 21 years due to hypotension when she was undergoing dialysis. Her mother had 2 abortions and one still birth before the girl was born.

On examination she had growth retardation. Her height was 129.7 cm and she weighed 22.1 kg (both were below the 0.2nd centile). She had severe acanthosis nigricans on the back of her neck and in the axillae (Figure 1). Her abdomen was protruberant and there was loss of subcutaneous fat on her buttocks. She had excessive body hair (Figure 2) and mild clitoromegaly. Breast and pubic hair distribution was suggestive of a Tanner stage 4 of pubertal development. Teeth showed dental dysplasia (Figure 3).

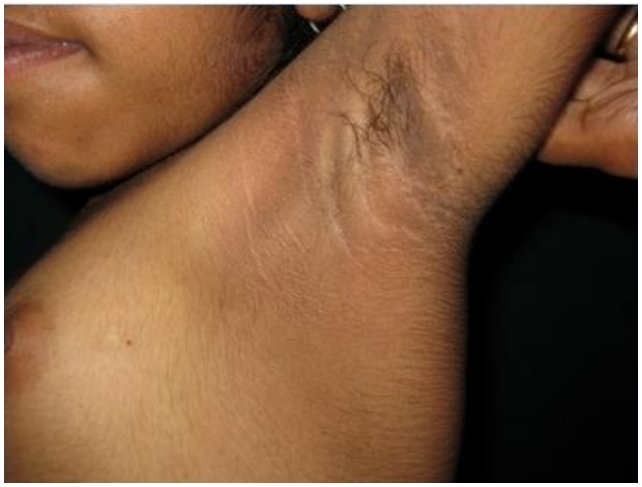

Figure 1: Severe acanthosis nigricans in the axillae.

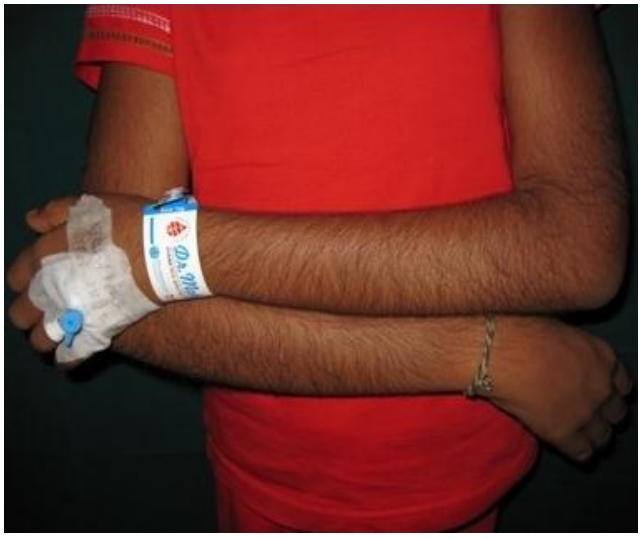

Figure 2: Excessive body hair on forearms

On investigations, her blood sugars were very high (500-600 mg/dl) with ketonuria (++) and mild ketonemia. C-peptide however showed fairly good pancreatic reserve with a fasting value of 0.9 ng/ml and stimulated value of 2.5 ng/ml. Serum sodium was 127 mmol/l, potassium 4.7 mmol/l and bicarbonate was 27 mmol/l. Sodium level improved with intravenous fluids and were normal on discharge.

Ultrasound abdomen was normal (including the ovaries and the uterus). Urea was 6.4 mmol/l, creatinine was 35.4 µmol/l, estimated protein excretion was < 200 mg/day and microalbuminuria was 11 µg/mg creatinine. Lipid profile was normal and hemoglobin was 160 g/l (9.92 mmol/l). Chest X-ray and abdominal X-ray were normal. Serum adiponectin levels were 23.1 µg/ml (normal range 3-30 µg/ml).

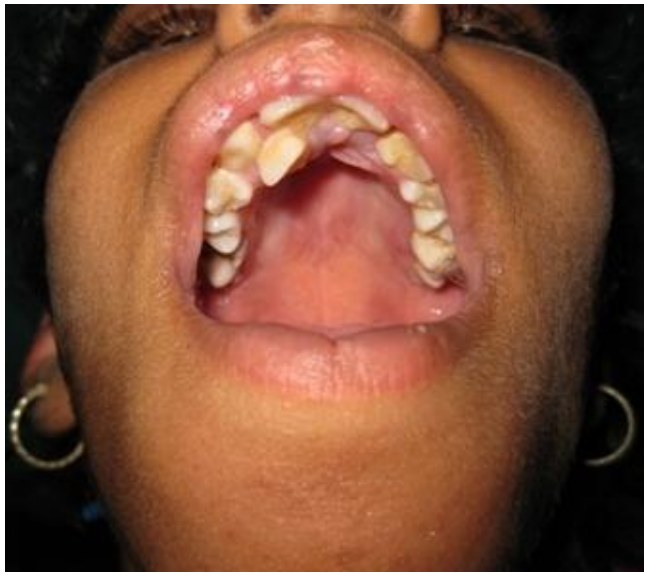

Figure 3: Dental dysplasia

For performing molecular genetic studies of the INSR gene, patient's blood sample was collected and DNA was extracted by phenol-chloroform method. Primers for all the 22 exons were designed using Primer 3 software. Amplification was done by PCR (ABI 9700, Foster City, USA) followed by purification using Exo-SAP (Fermentas). All the 22 exons including exon/intron boundaries were sequenced using Big Dye Terminator chemistry on ABI 3500 genetic Analyzer (Foster City, USA). Primer sequences and conditions were available upon request. We identified a known coding region mutation Pro220Leu (P220L, c.659C>T) in the homozygous state in exon 3 of INSR gene in case of proband and in heterozygous state in both parents. Prediction analysis was performed by online bioinformatics tools SIFT and PolyPhen2.

Her insulin doses were increased from 125 units (5.1 units/kg/day) to 155 units (6.3 units/kg/day) after which her sugars ranged between 200-500 mg/dl (with a fasting of around 220-230 mg/dl and postprandial of around 480-490 mg/dl). She was also commenced on pioglitazone 15 mg twice a day and metformin

500 mg twice a day to combat the insulin resistance. Nutritional recommendations and exercise counseling were also done.

She was later discharged with a hospital stay of 4 days.

Conclusion

A number of syndromes are associated with insulin resistance like Type A and Type B insulin resistance syndromes, Leprechaunism, Lipodystrophy and Rabson Mendenhall syndrome (RMS), out of which type A insulin resistance syndrome, leprechaunism and RMS are caused by mutations in the insulin receptor gene.

Previous studies have shown the Pro220Leu mutation of the INSR gene was found in patients with severe insulin resistance (4) but this mutation has been detected in a patient with Rabson Mendenhall syndrome for the first time in India. The residue 220 is present between receptor L domain and the furin like cysteine rich domain of INSR protein. Previous studies have reported mutations in this region of INSR gene in patients with severe insulin resistance syndrome. The prediction analysis on bioinformatics tools (SIFT and PolyPhen2) showed that the mutation Pro220Leu could probably damage the INSR protein. The mutation Pro220Leu is found in heterozygous state in both the parents and their marriage was consanguineous.

Rabson and Mendenhall in 1956 reported 3 siblings with dental and skin abnormalities, abdominal distension, phallic enlargement, early dentition, coarse senile faces, hirsuitism, mental precocity, prognathism, thick fingernails and acanthosis nigricans (5). Our patient was noted to have all these features, except mental precocity. She also had growth retardation. This is because patients have intrauterine and postnatal growth restriction (due to defective mitogenic action of insulin). Children with RMS can develop diabetic ketoacidosis. These children have initially paradoxical fasting hypoglycemia due to the extremely elevated levels of circulating insulin at the time of fasting coupled with prolonged half-life of the hormone and postprandial hyperglycemia, but eventually develop constant hyperglycemia from a progressive decline of endogenous insulin secretion and later develop constant severe and intractable diabetic ketoacidosis (3). Our patient had good insulin reserve at the time of presentation shown by a fairly good fasting and stimulated C peptide levels.

Patients with Type A insulin resistance syndrome can be of either sex and typically have early onset of diabetes with severe inherited insulin resistance, acanthosis nigricans, hirsutism, in the absence of autoantibodies to the insulin receptor (IR) (6, 7, 8). Type A insulin resistance syndrome and RMS have overlapping features but different clinical courses.

Type B insulin resistance syndrome is an autoimmune condition with anti IR antibodies being the hallmark of this syndrome (6, 7, 8). These patients commonly present in middle age and show features of severe insulin resistance (acanthosis nigricans, abnormal glucose homeostasis etc) and autoimmunity (vitiligo, alopecia areata etc).

The lipodystrophy syndromes are a diverse group of disorders characterised by severe insulin resistance and are associated with severe hypertriglyceridemia (6, 7, 8). These syndromes have been sub classified according to the extent (partial or generalized), the location and the age of onset (congenital or acquired). Congenital lipodystrophy is characterized by extreme scarcity of fat in subcutaneous tissue, whereas acquired lipodystrophy is progressive and sometimes triggers with an infectious prodrome (8).

Leprechaunism presents with paradoxical fasting hypoglycemia, profound hyperinsulinemia and postprandial hyperglycemia. They have typical facial features with flaring nostrils, low set ears and micrognathia. Physical features typically include stunted growth. Few of these infants live beyond the first year of life, although a few may survive until adolescence (6, 9).

Drug therapy for patients with severe insulin resistance syndromes is currently unsatisfactory. The combination of two insulin sensitizers (metformin and glitazone) is a well-known and validated therapy in patients with type 2 diabetes (6, 10). Patients with RMS have been

treated with high doses of insulin and insulin sensitizing drugs (11, 12). The introduction of multi drug therapy especially in the early phase might improve glycemic control, allows the use of lower doses of insulin and delay microvascular complications (11). A new approach for patients with RMS is the use of dipeptidyl-peptidase-4 (DPP-4) inhibitors, which has been found to have some additional advantages when used as combination therapy. The use of DPP4 inhibitors alone has not been proved to be beneficial (10).

Recombinant methionyl human leptin (r-metHuLeptin) therapy has shown clear efficacy in the treatment of severe insulin resistance in patients with lipodystrophy and low leptin levels. Cochran et al., have shown a 40-60% decrease in fasting serum glucose and insulin levels and improved glycosylated haemoglobin in two siblings with RMS treated with r-metHuLeptin therapy for 10 months (11).

High doses of IGF-1 has led to improvement in glycemic control and decrease in fasting insulin levels in short term studies but were not maintained in a 10 week trial (13). Recombinant leptin and / or IGF-1 might provide further therapeutic options for these patients in the event of secondary treatment failure (10). RMS patients have a poor prognosis, but survival is higher than in leprechaunism. Patients with leprechaunism generally die in the first two years of life and the survival in RMS is usually less than 20 years, although there are some documented cases with longer survival (11). With the advent of newer therapies, the future holds promise for patients with RMS.

Thus, RMS is a rare genetic disorder, with characteristic morphological features. There is no complete cure for the condition and the current treatments are difficult and not very promising.

Conflict of interest

None declared.

Acknowledgement

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