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Diabetes Mellitus Revealing a Rabson-Mendenhall Syndrome: A Case Report

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Abstract

Rabson-Mendenhall syndrome (RMS) is a rare autosomal recessive inherited disease marked by insulin resistance. Mutations in the insulin receptor gene seem to be the fundamental mechanism behind this type A insulin-resistant illness. Statural growth retardation, acanthosis nigricans, hypertrichosis, dysmorphia and coarse facial features, dysplastic dentition, enlarged external genitalia, postprandial hyperglycemia and paradoxical fasting hypoglycemia, severe hyperinsulinemia and potentially onset of ketoacidosis are the symptoms of this syndrome. Because there are few therapy choices for this illness and treating hyperglycemia is a difficult undertaking, a multi-disciplinary approach is crucial to managing this difficult clinical condition. We relate the case of a young male patient, after parental consent, with features of RMS suspected in the presence of dysmorphic syndrome and insulin resistance.

Keywords

Acanthosis Nigricans, Insulin Resistance, Diabetes, Hereditary

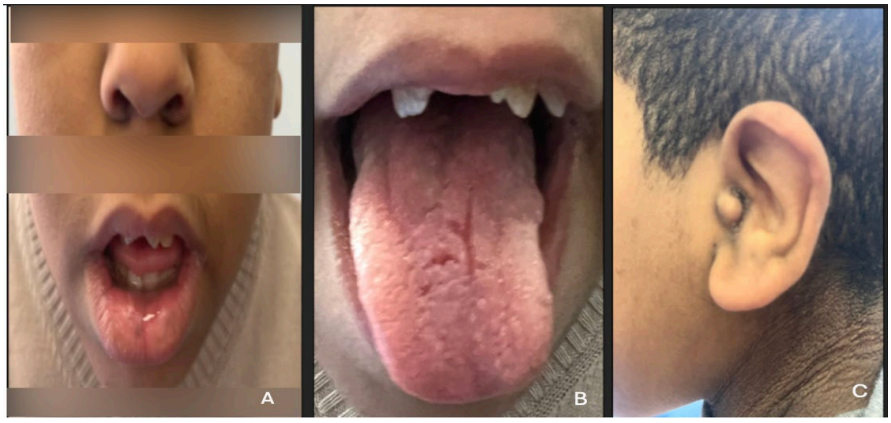
1. Introduction

First described in 1956 by Rabson and Mendenhall in a sibling with coarse facies and dermatological and dental abnormalities, Rabson-Mendenhall syndrome is a rare, autosomal recessive disease. After fasting hypoglycemia in early life, there will be hyperglycemia and ketoacidosis due to islet β-cell depletion, causing a progressive decline in insulin levels. This case is presented to outline and describe the broad spectrum of manifestations of this syndrome and its treatment.

2. Case Report

An 08-year-old boy, second of three siblings, born at full term from a first-degree consanguineous marriage, weighing 2.1 kg at birth. One of his sisters died 40 days after birth. He has been treated in dermatology since the age of 03 for acanthosis nigricans, has a history of repeated infections, notably enucleation of the left eye following a perforated abscess at the age of 02, and repeated ear infections. He has been treated in ophthalmology for cataracts of the right eye and was referred to the Department of Pediatric Endocrinology, Diabetology and Metabolic Diseases of Hassan II University Hospital, Fez, for investigation of a polyurea-polydipsic syndrome. There is no history of serious diseases in the family.

Physical examination revealed a stature-weight growth delay (height: −3 SD and weight: −2 SD) and body mass index 15.8 kg/m^2, with a dysmorphic face featuring a small head, dense hair, large nose, thickened lips, a cracked tongue, and large protruding ears (Figure 1).



A: Large nose and thick lips; B: Cracked tongue; C: Large protruding ears.

Figure 1. Dysmorphic face.

Teeth were irregular and the abdomen was prominent. Dermatological examination revealed acanthosis nigricans over the entire neck, thick finger nails and coarse hands (Figure 2).

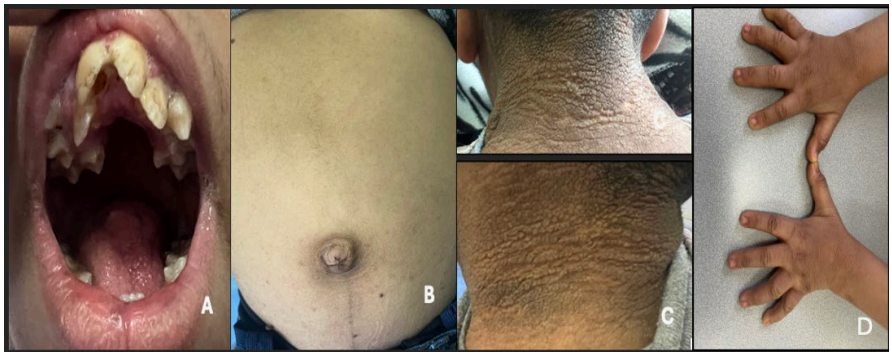


Figure 2. A: Irregular teeth; B: Prominent abdomen; C: Acanthosis nigricans; D: Thick finger nails and coarse hands.

The boy showed normal mental development. The results of the abdominal, neurological, pulmonary, and cardiovascular examinations seemed to be normal. Examining the external genitalia revealed a 7.3 cm penis, pubic hair and Tanner stage 1 testicles.

Biologically, blood counts, renal and liver functions were normal. Glycated hemoglobin was 10.2%, with blood glucose levels ranging from 274 mg/dl to 326 mg/dl with no episodes of fasting hypoglycemia, and urine dipstick showed positive glycosuria without ketonuria. Autoimmunity tests came back negative, with a C-peptide level of 3.43 ng/ml (0.8 - 3.5 ng/ml). The patient was put on insulin (basal-bolus) and Metformin chlorydrates 1500 mg/day. The patient did not undergo genetic testing due to lack of resources.

RMS was diagnosed based on these findings.

3. Discussion

Rabson-Mendenhall syndrome is an uncommon disease, its exact prevalence has not been assessed. It is characterized by severe insulin resistance, which can affect both men and women. RMS is an endocrine condition due to mutations in the alleles of the insulin receptor INSR, preferentially impacting children born to consanguineous parents [1]. Our patient is an 8-year-old boy from a 1st-degree consanguineous marriage.

The INSR gene, which has 21 introns and 22 exons, is found in 19p13.2-13.3. It consists of 2α and 2β subunits in a tetramer. α subunits are encoded by exons 1 to 11, and β subunits by exons 12 to 22 [2]. According to Kadowaki and colleagues, INSR mutations decrease the number of receptors on the cell surface by delaying the receptor's post-translational processing and delivery to the plasma membrane. The target cell developed insulin resistance as a result of the mutation of INSR, which also decreased the receptor's affinity for insulin [3]. After early fasting hypoglycemia, hyperglycemia and ketoacidosis occur due to insulin-secreting β-cell depletion, causing a progressive decrease in insulin levels [4].

Growth retardation during pregnancy and after delivery, dysmorphia, clitoromegaly in females and enlarged phallus in males, nephromegaly and abnormalities of the skin, teeth and nails are possible symptoms. Hypertrichosis, acanthosis nigricans, and polycystic ovaries are some of the characteristics linked to RMS that might result from the body's attempt to compensate for insulin resistance by secreting more insulin (hyperinsulinism) in these patients [1]. Our patient presented with intrauterine growth retardation, severe stature-weight growth delay, dysmorphic facies, acanthosis nigricans covering the entire neck and an enlarged penis.

As this disease progresses, insulin levels progressively decline, resulting first in constant hyperglycemia, and then in constant ketoacidosis [2]. This gradual deterioration is similar to that seen in those with type 2 diabetes, although it happens more quickly [1]. Our patient presented with features of persistent hyperglycemia, with poorly controlled diabetes and very high glycated hemoglobin levels.

Unfortunately, treatment of RMS patients is extremely difficult due to poor metabolic control, leading in a shortened life expectancy and the development of complications from diabetes. It is evident that the lack of data based on various treatment procedures is caused by the literature's scant experience with RMS patients [5]. So, there is no particular treatment. The goal of therapy is to maintain as stable blood glucose levels as feasible. Although dietary and activity changes have reduced glucose intolerance, it is unknown if these changes have any bearing on extremely insulin-resistant people [6]. Normal dosages of insulin are ineffective. However, very high doses (up to 9 U/kg per hour) or insulin sensitizers or secretagogues can have negligible effects, but this treatment is usually fruitless [7] [8]. As an example, a 17-year-old boy with RMS experienced a gradual improvement in glycemic control and short-term success with a multimodal treatment regimen that included dipeptidyl-peptidase-4 inhibitors in addition to two insulin sensitizers (pioglitazone and metformin). Additionally, this patient received dietary guidance and was urged to exercise [9]. Our patient was treated with metformin chlorydrate and insulin, basal bolus regimen of insulin Degludec and rapid human insulin at a dose of 2.66 IU/kg/day, with persistent imbalance despite adherence to hygienic-dietary measures and good therapeutic compliance.

In case of insulin resistance, recombinant human IGF-I (rhIGF-I) therapy, either by itself or in conjunction with its binding protein (IGFBP-3), has been shown to be useful. By using the IGF-I receptor to signal, rhIGF-I therapy may enhance the disposal of glucose. The effect of IGF-I on the pancreatic B-cells may be crucial for sustaining insulin production. Additionally, the same medication raises these individuals' c-peptide levels [10]. While high doses of recombinant human insulin-like growth factor-I (rhIGF-I) have been employed for treating patients with ketoacidosis and have improved their condition in some cases [11], the administration of recombinant human growth hormone and recombinant human IGF-1 is not related to positive results in terms of growth [12].

In these patients, the use of recombinant human methionyl leptin (r-metHu-Leptin) improved glycemia and insulin tolerance, fasting hyperglycemia, and hyperinsulinemia [13]. Metreleptin, a kind of recombinant methionyl human leptin, is a key indicator of satiety and has been demonstrated to enhance insulin-stimulated peripheral and hepatic glucose metabolism in individuals with severe insulin-resistance. The mechanism by which Metreleptin improves glucose in RMS may be that subcutaneous injections of the hormone reduce food intake and energy storage in patients with congenital leptin deficiency and lipodystrophy and changed central nervous system activity in areas linked to hunger and satiety [14]. Cochran and colleagues saw improvements in glycated hemoglobin and a 40% - 60% reduction in fasting blood glucose and insulin levels after giving r-metHu-Leptin to two siblings with RMS for ten months [11].

Acanthosis nigricans also disappears after the hyperinsulinemic condition is solved. However, benign acanthosis nigricans can be treated with podophyllin or topical keratolytics. For some people, topical or oral retinoids may also be helpful. Tretinoin 0.1% gel applied twice a day for two weeks can yield positive

results. Patients with acanthosis nigricans and insulin resistance have also been found to benefit from ketoconazole, presumably as a result of decreased insulin resistance [15].

4. Conclusion

RMS is a hereditary disease often misdiagnosed due to its low prevalence, with a challenging and unsatisfactory therapy, with a life expectancy of only a few years. The early mortality is due to the complications of insulin-resistant diabetes mellitus. A team of professionals, including surgeons, pediatricians and dentists, must work together to provide thorough, multidisciplinary treatment. Clinical results for these patients may be enhanced by new gene therapy studies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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