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Case report

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Rabson-Mendenhall syndrome: A rare case with severe insulin resistance

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Abstract

A rare hereditary cause of insulin resistance, Rabson-Mendenhall syndrome (RMS) is manifested by extreme insulin resistance caused by mutations in the insulin receptor (INSR) gene. The characteristics of RMS are retarded growth, dysmorphisms, hirsutism, enlarged genitalia, acanthosis nigricans, dysplastic dentition, hyperglycemia, elevated insulin level, and hyperplasia of the pineal gland. RMS patients usually present in childhood and most affected patients usually survive till the second decade of life. We are presenting here a unique case of a 10-year-old girl with very high blood sugar and crowding of teeth. She developed classical symptoms of diabetes for the last three years. On examination, she had syndromic coarse facies, prognathism, gingival hyperplasia, larger lower lip, hyperdontia, hyperpigmented skin, hypertrichosis, severe acanthosis nigricans & dystrophic nails. Biochemical investigations revealed insulin resistance by high fasting insulin, and high normal C-peptide with very high Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). She was treated with insulin with insulin sensitizer-Metformin & Pioglitazone but her blood glucose was still poorly controlled. *[J Assoc Clin Endocrinol Diabetol Bangladesh,* July 2025;4(2)*: 80-84]*

Keywords: Rabson-Mendenhall syndrome, Acanthosis nigricans, Hypertrichosis, Insulin resistance

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Introduction

Rabson-Mendenhall syndrome (RMS) is a rare genetic cause of insulin resistance which is inherited as an autosomal recessive trait. It occurs in less than one in a million people. Because of mutations in the insulin receptor (INSR) gene, RMS is characterized by extreme insulin resistance. The production of insulin gradually decreases over time in patients suffering from RMS which leads to the development of constant hyperglycemia & ultimately to diabetes mellitus. Patients suffering from RMS undergo developmental problems in different parts of the body as a result of extreme insulin resistance. Short stature, absence of subcutaneous fat, dental abnormalities, hirsutism, multiple ovarian cysts, and enlarged nipples and genitalia are all common symptoms of RMS patients. Severe acanthosis nigricans is a striking feature of insulin resistance in patients of RMS.[1] RMS is one of the subtypes in a group of disorders recognized as inherited insulin resistance syndromes (IIS). The spectrum of inherited insulin resistance syndrome also belonging Donohue syndrome and type A insulin resistance syndrome. Usually Type A insulin resistance syndrome is not identified until puberty, while Donohue syndrome is typically deadly before the age of two. RMS is intermediate in severity between those two conditions. In the end, these patients acquire severe insulin-resistant diabetes, which necessitates extremely high insulin dosages to reach normoglycemia. Phenotypic classic features and genetic testing confirm the diagnosis of RMS. In early life, these patients exhibit symptoms and signs and they often survive into their

second or third decade of life. Diabetic complications such as diabetic ketoacidosis usually cause early death of these patients.[2]

Case summary

A 10-year-old girl, the second issue of a non-consanguineously married couple with no significant perinatal history except low birth weight, was referred from dental OPD with severe hyperglycemia. She developed polyuria, polydipsia, and polyphagia with weight loss for three years and crowding of teeth since childhood. She also had a history of an increase in body hair and gradually worsening blackish darkening of the neck and body folds. Her mother had a history of type 2 diabetes but she had no dysmorphic features. Her siblings were in good health.

The patient was apparently short and malnourished. She was 125 cm tall (below the 5th percentile) & her weight was 21 kg (below the 5th percentile) with a body mass index (BMI) of 13.46 kg/m^2. Her arm span and upper segment lower segment ratio were 123 cm and 0.9, respectively. Her waist circumference was 59 cm & hip circumference was 58 cm. Her blood pressure was 110/80 mm of Hg. Her face was coarse and triangular, and she had prognathism, thickened lips, and a depressed nasal bridge (Figure-1). She had abnormal teeth formation with hyperdontia, a deep fissured tongue, and a high-arched palate (Figure-2). She had severe acanthosis nigricans over the nape, shoulder, axilla, and also over the dorsum of the feet & hands (Figure-3), generalized hypertrichosis & thickened nails (Figure-4). She had a distended abdomen with

Table-I: Investigation profile of the patient

Investigation	Result	Normal Range
Complete Blood Count	Haemoglobin:13.3 g/dL,	-
	WBC count: 7000/cmm	-
	Platelets: 3,70,000/cmm	-
Urine routine examination	Sugar: ++++	-
	Protein: Nil	-
	Ketone body: Nil	-
Fasting blood sugar	12.5 mmol/L	-
2 Hour after breakfast	18.2 mmol/L	-
HbA1c	15.2%	-
Fasting Insulin	20 uU/mL	2-10 uU/ml
C-Peptide	2.37 ng/mL	0.7-3.6 ng/mL
HOMA-IR	11.11	<2.5
Serum creatinine	0.40 mg/dL	0.5-1.2 mg/dl
SGPT	29 IU/L	0-55 U/L
Fasting lipid profile	Total Cholesterol: 165 mg/dL	-
	Triglyceride: 120 mg/dL	-
	HDL-Cholesterol: 40 mg/dL	-
	LDL-Cholesterol:101 mg/dL	-
Serum electrolyte	Na^+ :133 mmol/L,	-
	K^+ :3.56 mmol/L,	-
	Cl^- :95.8 mmol/L,	-
	T-CO_2 :31.6 mmol/L	-
Serum calcium	9.6 mg/dL	8.5-10.5 mg/dl
Basal cortisol	10.6 ug/dL	-
S. TSH	0.5 uIU/mL	0.7-5.70 uIU/mL
FT4	12.9 pmol/L	0.89-1.76 ng/dl
X-ray for bone age	Correspond to 7-8 years of age	-
Ultrasonography of the whole abdomen	Bilateral early renal parenchymal disease, left renal cortical cyst	-
Doppler echocardiography	Normal	-

HbA1c: Glycated Hemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; SGPT: Serum Glutamate Pyruvate Transaminase; Na^+: Sodium, K^+: Potassium, Cl^-: Chloride, T-CO_2: Total carbon-di-oxide; S.TSH: Serum thyroid stimulating hormone, FT4: Free thyroxine

Figure-1: Appearance of the patient

Figure-2: Hyperdontia with deep fissured tongue

Figure-3: Severe acanthosis nigricans

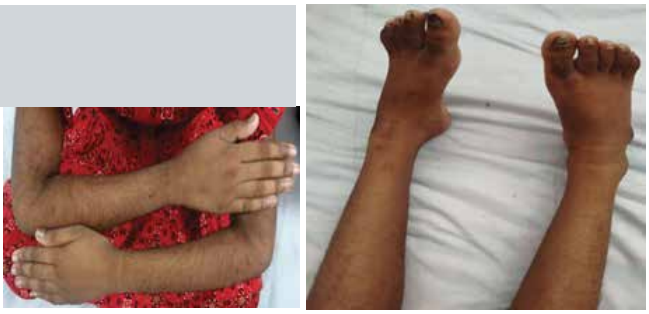

Figure-4: Hypertrichosis with nail dystrophies

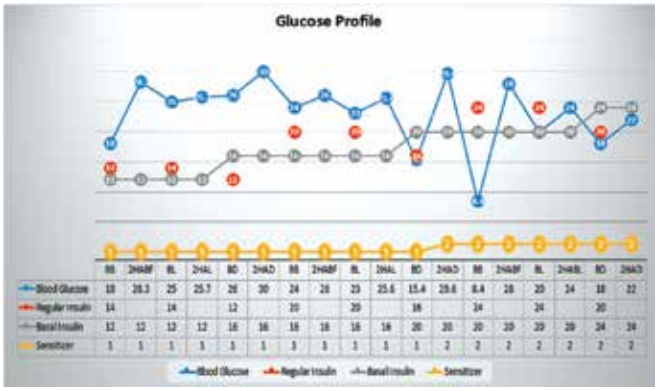

Figure-5: Glucose profile of the patient

noticeable subcutaneous fat loss. But there was no muscular hypertrophy. She had delayed growth in comparison to her chronological age. Her Tanner staging was B1P1. Genitalia examination revealed mild clitoromegaly (clitoral index 42 mm^2). The fundoscopy examination was normal. Systemic examination was not contributory except for expressive aphasia & hearing impairment. Biochemical investigations revealed insulin resistance by high fasting insulin, and high normal C-peptide with very high Homeostatic Model

Assessment of Insulin Resistance (HOMA-IR) (Table-I). Her fasting & post-prandial blood sugar were 12.5 mmol/L & 18.5 mmol/L, respectively. Her routine liver function, renal function, and blood count tests were within normal ranges. Glycosuria was present in routine urine analysis. She was euthyroid & eucortisolemic. Her bone age was delayed and an ultrasonogram of her abdomen revealed early renal parenchymal disease (Table-I). Based on these typical phenotypic features and biochemical findings a diagnosis of RMS was made. In spite of treatment with a total of 100 units of insulin (more than 3 units/kg body weight) with insulin sensitizer metformin & pioglitazone, her postprandial blood glucose was still poorly controlled (Figure 5).

Discussion

An inadequate glucose response to a certain insulin concentration is referred to as insulin resistance.[3] Insulin resistance is primarily caused by genetic abnormalities in insulin signaling, excess cortisol, growth hormone, catecholamines, glucagon, and obesity. Extreme insulin resistance is seen in patients having genetic syndromes. At first, the patients have normal blood glucose with a concomitant increase in insulin levels and subsequently, have a higher postprandial sugar before the development of well-sustained hyperglycemia. This is due to the fact that hepatic steatosis or insufficient hepatic insulin clearance is present in persons having INSR defects. Very few patients having activated autoantibodies against the INSR may present with hypoglycemia.[4, 5, 6] In 1956 Rabson and Mendenhall first described the features of this syndrome as abdominal distension, coarse facial features, early dentition, hirsutism, penile enlargement, pineal hyperplasia, and dental and skin abnormalities which were observed in three siblings. RMS is a very unusual form of inherited insulin resistance that is linked to autosomal recessive trait patterns with diverse penetrance. Initially, there is fasting hypoglycemia and then there is typically persistent hyperglycemia by the age of four, and by the age of six, there may be persistent ketoacidosis. At first, insulin levels are very high, but as people mature, they fall but stay above normal.[7, 8]

Because of polymorphisms in the insulin receptor gene, a variety of hereditary insulin-resistance disorders arise, from severe Leprechaunism to Type A insulin resistance. RMS usually have an intermediate phenotype and patients with RMS usually survive more than one year but they have a limited life expectancy up to puberty.[9,10,11] Both RMS and leprechaunism (Donohue syndrome) are autosomal recessive diseases characterized by aberrant insulin receptor alleles. Those two conditions have almost similar clinical features. Affected infants may have characteristics facial and head deformities. They are underweight at birth, have skin abnormalities, and have abnormally enlarged breasts and clitoris in females and penis in males.[12] Leprechaunic infants typically do not survive past their first year of life.[13] The symptoms of leprechaunism are more severe in infants. Fasting hypoglycemia is the main problem in leprechaunic infants, and they do not develop ketoacidosis. RMS is less severe and is characterized by coarse facial characteristics, gingival hyperplasia, pineal hyperplasia, early and dysplastic dentition, and survival past one year of age make differences between RMS from leprechaunism.[9,10,11]

There are similarities between the presenting case's clinical characteristics-acanthosis nigricans, thick nail and hypertrichosis, hyperdontia, and hyperinsulinemia with the syndrome's first original description.[14] The clinical findings of coarse facial features, dry skin, thickened lips, deep fissured tongue, and depressed nasal bridge are well fitted with the findings reported by Alaei et al.[15] Additionally, there are similarities between the dental findings of this patient with the publication of Rabson et al.[7] All the features of RMS are present in our patient except sexual precocity. She also had expressive aphasia & hearing impairment. Consultation from the ENT department was taken, and they diagnosed as prelingual deafness and expressive aphasia which is not described in any previous reports. The explanation of retarded growth of this patient may be due to growth restriction both during pregnancy and after delivery as a result of impaired mitogenic action of insulin. Though RMS can be diagnosed clinically by typical phenotypic features and biochemical abnormalities, it is our limitation that genetic studies for diagnosis of RMS could not be done due to financial constraints. INSR gene mutation occurs in RMS which is usually detected by single-gene sequencing. Besides this, next-generation sequencing (NGS) for panels for insulin resistance syndrome and whole-exome sequencing (WES) can be done if standard genetic tests do not identify the mutation.

Currently, there are no particular treatment options for patients suffering from RMS. In general, the treatment is symptomatic. Keeping blood glucose levels under control is the aim of treatment. Conventional normal doses of insulin can't achieve the blood glucose target. To control blood glucose up to 9 U/kg per hour insulin

may be needed. Along with Insulin, metformin, and pioglitazone are proven effective therapy in the treatment of patients with RMS. Glycemic control may be enhanced by the institution of multidrug therapy, especially at the onset of disease and it permits lower dosages of insulin. As a result, the development of complications may be delayed. Some affected patients showed improvement when high doses of recombinant human insulin-like growth factor I (rhIGF-I) were used. Recombinant methionyl human leptin (r-metHuLeptin) administration in some patients with RMS has also been shown to improve glucose and insulin tolerance, hyperinsulinemia, and fasting hyperglycemia.[1]

Detailed explanation of the condition was given to the parents of our patient. As RMS is an autosomal recessive condition, parents are typically carriers, so advice on screening of other family members was given and future chance of transmitting the disease to offspring was explained.

Conclusion

As RMS is genetically inherited, its treatment is not satisfactory till now. To enhance the clinical results for these individuals, more advanced studies focusing on gene therapy are required. More attention should be given to genetic disorders and their detection in regions where resources for genetic study are limited and are in their initial stage.

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Disclosure

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Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Written informed consent was obtained from the patient. All methods were performed in accordance with the relevant guidelines and regulations.

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