Case Report

Rabson-Mendenhall syndrome: a rare case of severe insulin resistance

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ABSTRACT

Insulin resistance syndromes are a heterogeneous group of disorders with variable clinical phenotypes, associated with increased blood glucose and insulin levels. A 20-year-old female, diabetic for 12 years, reported with hyperglycemia not responding to high dose of insulin; therefore, insulin dosage was increased but did not lead to appropriate glycemic control. Investigations revealed hyperglycemia (random blood glucose 23 mmol/L) glycosylated hemoglobin (HbA1c) 9.2%. Ultrasonogram of the abdomen showed prominent ovaries with fatty liver. Echocardiography revealed mild mitral, pulmonary and tricuspid regurgitation and pulmonary hypertension. Based on the clinical features, skin changes and the onset of type 2 diabetes mellitus, Rabson-Mendenhall syndrome (RMS) was considered. In last admission, she was admitted for hyperglycemic control and treated with intravenous fluids, insulin infusion, metformin, pioglitazone, linagliptin, hydroxychloroquine, sulphonylurea, antibiotics. There is no complete cure for the condition and the current treatments are difficult and not very promising.

Key words: *acanthosis nigricans, diabetes, insulin receptor, insulin resistance, Rabson-Mendenhall syndrome.*

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INTRODUCTION

Rabson-Mendenhall syndrome (RMS) is a genetic syndrome epitomized by severe insulin resistance, where there is an inappropriate response to insulin by the tissues and organs. It is an extremely rare autosomal recessive disorder. Severe insulin resistance in people with RMS affects the development of many parts of the body. Affected individuals present with small stature, lack of subcutaneous fat, muscle atrophy, dental abnormalities, hirsutism, polycystic ovaries and enlargement of the nipples and genitalia. The skin in body folds and creases becomes thick, dark and velvety called acanthosis nigricans.[1] Severe insulin resistance is caused by genetic defects of the insulin receptor gene (Type A syndrome, Leprechaunism and RMS) or by the presence of circulating auto-antibodies that disrupt the normal functions of the insulin receptor (Type B syndrome). RMS differs from Leprechaunism in the presence of premature and dysplastic dentition, coarse facial features, and pineal hyperplasia. These patient ultimately develop severe insulin-resistant diabetes requiring very large doses of insulin to achieve normoglycemia. The diagnosis encompasses both teenage and adolescents who are not obese but have severe insulin resistance and acanthosis nigricans in the absence of insulin receptor autoantibodies.[2] Here, we present a 20-year-old girl with clinical features of RMS who presented with uncontrolled blood glucose with short stature and delayed puberty.

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CASE REPORT

A 20-year-old Bangladeshi female presented with complaints of poorly controlled diabetes. The patient's earlier medical records indicated that she was diagnosed as a case of type 2 diabetes mellitus at her 8 years of age. Her glycemic level was not at desirable level most of the time, evidenced by regular self-monitoring of blood glucose records at home, inspite of proper lifestyle modification and multiple oral antidiabetic medications and insulin. In last admission, she experienced hyperglycemic state without ketonuria and was treated with intravenous fluids, insulin infusion, metformin, pioglitazone, sulphonylurea, linagliptin and other supportive treatments as needed. But it was difficult to control her blood glucose with use of human insulin tried first and by use of analog insulin next. The parents of this patient were first consanguine; the father's height is 175 cm and mother is 152 cm tall. The patient has a younger sister and a younger brother; both of her siblings have features of genetic syndrome (short stature, webbed neck, scoliosis, partial ptosis, clawing of fingers) but not yet evaluated properly. There was no history of diabetes mellitus or insulin resistance in any of her family members. Her mother availed herself regular antenatal care. She underwent a domicile delivery to give birth to the patient at term with birth weight 3 kg and the baby (our patient) was properly immunized at her childhood. She was developmentally normal except having history of early dentition. She had delayed puberty (menarche at 17 years) with irregular period since menarche.

The patient was poorly built and undernourished. Her height was 136 cm and the weight 27 kg with body mass index (BMI) 15.8 kg/m² at the time of admission. Her arm span was 135 cm and upper segment lower segment ratio 0.8. Her blood pressure was 140/90 mm Hg. She has triangular face with prognathism (Figure 1), thickened lips, depressed nasal bridge (Figure 2), hypertelorism, abnormal teeth formation with hyperdontia (Figure 3), deep fissured tongue, high arched palate and cubitus vulgas with dry coarse and creased skin, dark and velvety appearance, especially over nape (Figure 4), shoulder, axilla, dorsum of hand and feet (Figure 5) with multiple skin tags. Subungual hyperkeratosis was also noted in toenails (Figure 6). There were no signs of icterus, cyanosis, clubbing, lymphadenopathy but patient was moderately anemic

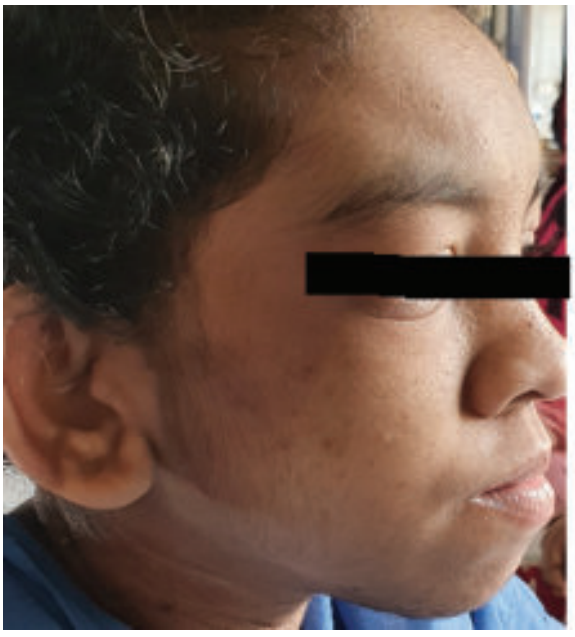

Figure 1 Coarse facies with prognathism and hirsutism of the patient

Figure 2 Triangular coarse face and depressed nasal bridge

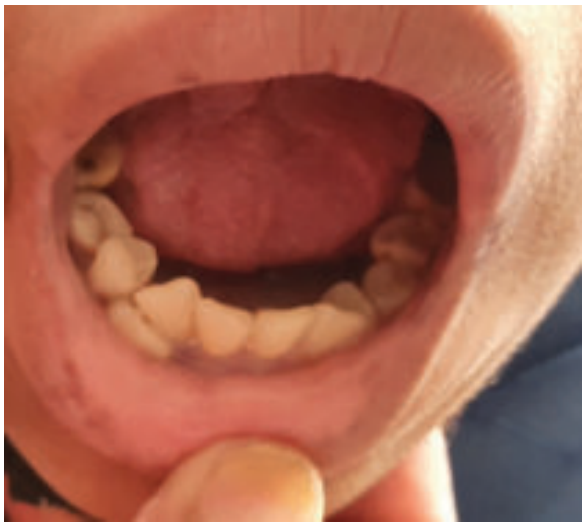

Figure 3 Malocclusion with hyperdontia

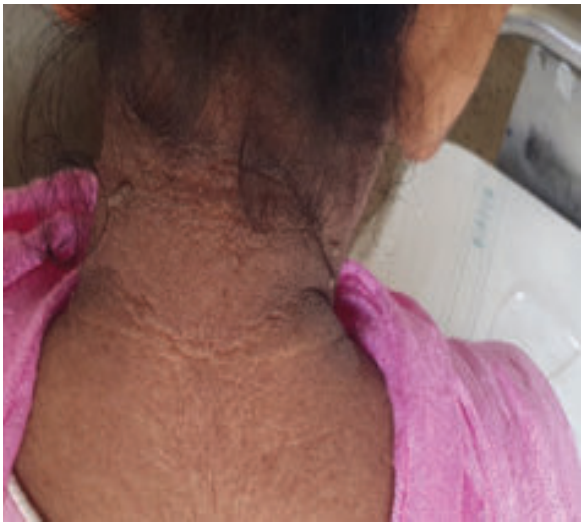

Figure 4 Acanthosis nigricans on the nape with skin tag

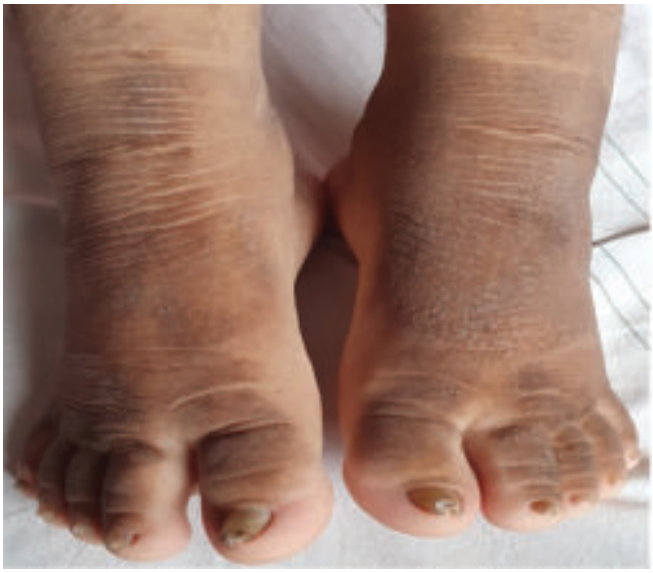

Figure 5 Acanthosis nigricans on the dorsum of foot extending to lower leg extending to lower leg

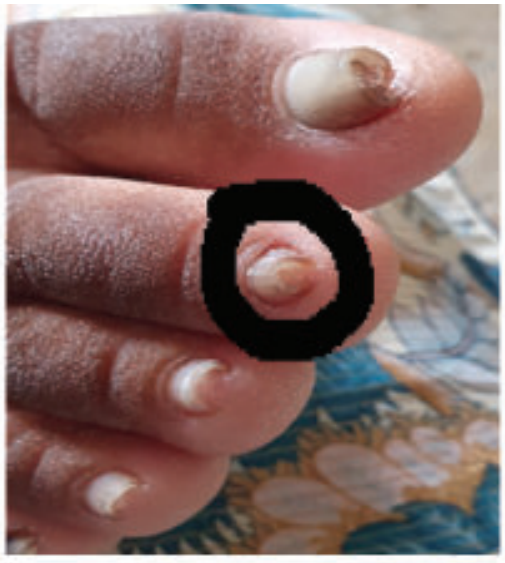

Figure 6 Subungual hyperkeratosis

and pitting edema was present. Her growth was delayed in relation to chronologic age but there was no evidence of muscular hypertrophy. Her pubertal staging was B4 P3 and modified Ferryman-Gallwey score was 13 with mild clitoromegaly (2 cm). Her investigations revealed (Table I) normal C peptide level with negative insulin autoantibody, her karyotype was 46, XX, skin biopsy reveal acanthosis nigricans. Her bone age corresponded to her chronological age and ultrasonography of abdomen revealed fatty liver and prominent ovaries. Inspite of treatment with multiple oral antidiabetic drug and a total 600 unit of insulin/day, she failed to reach the glycemic target. Hydroxychloroquine was added to her treatment with a goal to reduce insulin resistance.

Table I Investigations of the patient

Routine investigations			Special investigations	
1.	Hemogram		1. Insulin auto Ab	7.875 IU/ml(<20IU/ml)
	Hb	9.2 g/dl	2. AMH	4.47 ngm/ml
	ESR	31 mm in 1st hour	3. Ostradiol 17 B	109.79pg/ml (21-160 pg/ml)
	PCV	26.6 %	4. S. LH	6.51mIU/ml (1.80-11.78mIU/ml)
	RBC	3.33 ´10^{12}/L	6. FSH	5.34mIU/ml (3.03-8.08mIU/ml)
	WBC	7.76´ 10^9/L	7. ACTH	24.90pg/ml (8.3-57.8pg/ml)
	Platelet count	200× 10^9/L	8. Basal Cortisol	302.63nmol/L
2.	S. electrolyte		9. Anti Tg Ab	0.7IU/ml (<4.5= Negative)
	S. Na^+	140 mmol/L	10. Anti TPO Ab	<37 U/ml (<60= Neagtive)
	S. k^+	3.5 mmol/l	11. C-Peptide	6.34 ng/ml (1.20-3.40ng/ml)
	S. Chloride	103 mmol/L	12. Chromosome analysis(karyotype)	46, XX (female karyotype)
	S. TCO2	26 mmol/L	13. Skin Biopsy	Features of acanthosis nigricans
3.	S. creatinine	0.7 gm/dl		
4.	S. Total protein	53.5gm/L		
5.	S. Albumin	24.1 g/L		
6.	HbA1C	9.3 %		
7.	Lipid Profile			
	S. Cholesterol	308 mg/dl		
	HDL- Cholesterol	66 mg/dl		
	LDL-Cholesterol	256 mg/dl		
	Triglyceride	80 mg/dl		
8.	TSH	1.56 uIU/ml		
9.	F.T4	13.9 pmol/L		
10.	Urine R/E			
	Pus cell	6-10/HPF		
	RBC	0-2 /HPF		

DISCUSSION

In 1950, Mendenhall described a child with severe insulin-resistant diabetes[3] in whom, there was presence of hyperplasia of pineal gland at post-mortem. In 1956, Rabson and Mendenhall reported three siblings with extreme insulin-resistant diabetes, acanthosis nigricans, thick rapidly growing scalp hairs, phallic enlargement, precocious pseudo-puberty, markedly thickened nails, dental abnormality and pineal hyperplasia.[4] Later in 1975, West et al., described siblings with similar clinical features.[5]

Mutation in insulin receptor gene causes the severe insulin-resistant syndrome like Leprechaunism and Rabson-Mendenhall syndrome. Their metabolic feature includes fasting hypoglycemia, post-prandial hyperglycemia and extremely elevated insulin levels. Due to extreme insulin resistance, patient fails to respond to endogenous and exogenous insulin with intra-uterine and post-natal growth retardation leading to dysmorphic features, lack of subcutaneous fat, acanthosis nigricans and enlargement of genitalia, hirsutism, paradoxical fasting hypoglycemia and post-prandial hyperglycemia.[6] The define of insulin resistance is a state of a tissue in which a greater than normal amount of insulin is required to elicit a quantitively normal response.[7] Severe insulin resistance in an insulin-dependent subject might be suspected when requiring more than 200 units /insulin.[8]

Clinical features of the present case (acnthosis nigrican, hypertrichosis and thick nails, dental prematurity with

hyperinsulinemia) are well correlated with the original description of the syndrome.[9] Coarse facial appearance, macroglossia, thickened lips, depressed nasal bridge, and dry skin are well correlated with the findings reported by Alaei et al.[2] The dental findings are also well correlated with findings reported by Renuka et al.[10] Our patient was noted to have all the features of RMS, 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). Limitation of this case report is that genetic studies (mutation of INSR gene and chromosomal study by FISH) could not be performed due to the financial constraints of the patient's family.

The combination of two insulin sensitizers (metformin and glitazone) is a well-known and validated therapy in patients with type 2 diabetes.[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. Insulin, proinsulin, Insulin like growthfactor 1(IGF1)and Insulin like growthfactor (IGF2) show remarkable structural and impart sequence homology.[13] Receptors of insulin and IGF1 are related in structure and share common post-receptor signaling pathways.[14]So, insulin and IGF1 are capable of stimulating glucose uptake, glycogen synthesis and the inhibition of protein catabolism but because of lacks of IGF1 receptors on adipose tissue, IGF1 has little effect on this tissue.Therefore, rhIGF1 therapy in patients with severe insulin resistance may be effective.

Our patient is surviving 12 years after diagnosis of diabetes,make this case more rare. With the advent of newer therapies, the future holds promise for patients with RMS.

Conclusion

In this case a 20-year-old female with T2DM for 12 years presented with hyperglycemia not responding to high insulin dose due to severe insulin resistance, leading to inappropriate glycemic control. Based on the clinical features, skin changes and the onset of T2DM, RMS was considered. A larger focus is warranted on genetic diseases and their diagnosis, especially in a developing country like Bangladesh where facilities to diagnose genetic diseases are still evolving and are at a incipient stage.

Authors' contribution: FA drafted the manuscript, editing and review done by FA, all authors contributed in reviewing the manuscript.

Consent: The manuscript submitted to the journal with permission of the patient and her mother.

Conflicts of interest: Nothing to declare.

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