

Case Report

Rabson Mendenhall Syndrome; a Case Report and Review of Literature

Daniel Zamanfa^{1,*}, Fatemeh Mohamadi², Somayeh Rostami Maskopaii¹

¹Diabetes Research Center, Mazandaran University of Medical Sciences, Sari, Iran

²Research Department of Mazandaran University of Medical Sciences, Sari, Iran

Email address:

danielzamanfar@yahoo.com (D. Zamanfar), Mohamadi.f@yahoo.com (F. Mohamadi), Somayehrostami14@yahoo.com (S. R. Maskopaii)

*Corresponding author

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Abstract: Genetic disease is caused by a gene change. Genetic disease is one of the types of diseases affecting the personal, family and social life. One of the types of genetic disease is Rabson Mendenhall Syndrome. The Rabson Mendenhall Syndrome (RMS) was first described by Rabson and Mendenhall in 1956. Rabson Mendenhall syndrome is an extremely rare genetic disorder with autosomal recessive inheritance of unknown prevalence that is estimated to affect less than 1 per million people worldwide characterized by severe insulin resistance. The present study is a case report of a patient with Rabson Mendenhall Syndrome in Iran. A 6 year old girl presented with severe hyperglycemia and loss of consciousness and acidosis. In spite of taking large doses of insulin, her sugars were uncontrolled. She had severe acanthosis nigricans. There was associated growth retardation, dental dysplasia, distent abdomen, emaciated extremities and clitoromegaly. In last admission with diabetic ketoacidosis she was treated with intravenous fluids, insulin drip, metformin and also pioglitazone, antibiotics and other supportive treatments as needed, but unfortunately after few days this treatments could not save her and patient expired. There is no complete cure for the condition and the current treatments are difficult and not very promising.

Keywords: Diabetes Mellitus, Insulin Resistance, Rabson Mendenhall Syndrome

1. Introduction

The Rabson Mendenhall Syndrome (RMS) was first described by Rabson and Mendenhall in 1956. They described three siblings with Insulin resistant diabetes mellitus having characteristic facial, skin, skeletal and dental features [1]. The other names of this condition are pineal hyperplasia and diabetes mellitus syndrome and also pineal hyperplasia, insulin resistant diabetes mellitus and somatic abnormalities. Rabson Mendenhall syndrome is an extremely rare genetic disorder with autosomal recessive inheritance of unknown prevalence that is estimated to affect less than 1 per million people worldwide characterized by severe insulin resistance. Homozygous mutations in Insulin receptor gene (INSR) are responsible for this syndrome [2]. The locus of mutation in INSR gene is 19 p 13.3- p 13.2 [3].

Mutations in the insulin receptor gene produce a spectrum

of diseases including Donohue's syndrome (leprechaunism), Rabson Mendenhall syndrome and type A insulin resistance; patients with these conditions have several different characteristics [4]. RMS in severity is between Donohue syndrome (fetal before second year of life) and type A insulin resistance (which is often not diagnosed before adolescence). Severe cases are diagnosed at birth or in infancy due to the presence of signs of severe hyperinsulinaemia such as acanthosis nigricans, abnormal dentition, hyperandrogenism and pseudo-acromegaly [5, 6].

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 [4]. 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)

[7].

RMS is characterized by growth retardation, Failure to thrive, atrophy of muscles, coarse facies, widely spaced eyes, a broad nose and large low set ears, and skin manifestations such as hyperpigmentation, acanthosis nigricans and hypertrichosis. Dental abnormalities, enlarged phallus in males, clitoromegaly and multiple cysts on the ovaries in females, enlargement of nipples, genitalia, kidneys (nephromegaly), heart and other organs as penis in males, nephrocalcinosis, paradoxical fasting hypoglycemia, postprandial hyperglycemia, severe insulin resistance and hyperinsulinemia are other associated findings [7, 8].

2. Effective Mechanism of Insulin

Insulin receptors are heterotetrameric receptors consisting of two (α) and two (β) subunits. Insulin binds to the extracellular subunits of its receptor and activates the intracellular tyrosine kinase in the transmembrane subunits [3, 4]. Tyrosine kinase phosphorylates and recruits certain intracellular intermediates such as insulin-like substrates 1 and 2, Shc, and Gab1 [7]. These intermediate substances activate other signalling molecules like Growth factor receptor-bound protein 2, Cytoplasmic proteinNck, tyrosine phosphatase and the phosphoinositide-3 kinase, amplifying the initial effect generated by the insulin binding to its receptor. These complex interactions finally produce the expected insulin effects like uptake of glucose and amino acid by the cells, glycogenesis, fattyacid and cholesterol synthesis. In addition, insulin inhibits gluconeogenesis in the liver [4]. Any defects at any of the above mentioned steps of this complex pathway can lead to insulin resistance.

So in this patient the body may attempt to compensate for insulin resistance by increasing of insulin (hyperinsulinemia) but, with progression of disorder, insulin levels decrease and are no longer capable of suppressing glucose production and release by liver that resulting in constant hyperglycemia. Further decrease of insulin level compromise suppression of fatty acid oxidation and so constant ketoacidosis ensues [8].

3. A Genetic Factor

Although the molecular basis for extreme insulin resistance remains unknown in many patients, lipodystrophies and loss of function mutations in the insulin receptor gene are well established causes of this phenotype (Table 1) [9].

Table 1. Reported *INSR* mutations associated with Rabson Mendenhall syndrome [10-12].

No	<i>INSR</i> mutation
1.	Pro193Leu Pro193Leu
2.	Cys284Tyr Cys284Tyr
3.	Ser323Leu Ser323Leu
4.	Ile1116Thr Arg1131Trp
5.	Pro970Thr Arg1131Trp
6.	Arg1174Trp WT
7.	Asn878Ser Ala1162Val
8.	Cys159Phe Arg229Cys

No	<i>INSR</i> mutation
9.	Asn15Lys Arg1000X
10.	Arg209His Gly359Ser
11.	Arg86X Mu p. Asp261 _Leu262insLeuHisLeuVal
12.	IVS4-2A > G c. 2480-2487del
13.	Ile321Phe
14.	Ile348Phe, c. 1042A > T
15.	Pro220Leu
16.	c. 5C > G, c. 123. G > T, c. 165. G > A

4. Case Presentation

A 6 year old girl of Asian Iranian origin presented to us with poorly controlled diabetes. She didn't use appropriate doses of insulin and she presented to us with DKA and her HbA1c was grossly elevated at 13.3%.

She was born as the first child of parents. Her younger brother are healthy. She was pre term (32 week) at birth and was delivered by lower segment cesarean section (LSCS) with a birth weight of 1500 gr (IUGR). She was developmentally normal. She had history of icter and cholestasis and hypothyroidy in infancy.

On examination she had growth retardation. Her height was 97 cm and she weighed 10 kg (both were below the 3 centile). She had severe acanthosis nigricans on the back of her neck and in the axillae. Her abdomen was protruberant and there was loss of subcutaneous fat on her buttocks and exterimitis, and mild clitoromegaly. Teeth showed dental dysplasia. Lipid profile was abnormal (TG 1900 mg/dl, chol 300 mg/dl, VLDL 38 mg/dl, LDL 52 mg/dl, HDL 49 mg/dl) and hemoglobin was (14.4 mmol/l). Chest X-ray and abdominal X-ray were normal. Her TSH was 2.4 mIU/l and free T4 was 1.4 mIU/l. Her sugar controlled with high dose insulin and metformin 500 mg twice a day and pioglitazone 15 mg three times per day.

Her sugars ranged between (200-500 mg/dl) with fasting of around (200-400mg/dl) and postparendial (300-500 mg/dl).

In last admission with diabetic ketoacidosis she was treated with intravenous fluids, insulin drip, metformin and also pioglitazone, antibiotics and other supportive treatments as needed, but unfortunately after few days this treatments could not save her and patient expired.



Figure 1. Patient with Rabson Mendenhall Syndrome.



Figure 2. Patient with Rabson Mendenhall Syndrome.



Figure 3. Patient with Rabson Mendenhall Syndrome.



Figure 4. Patient with Rabson Mendenhall Syndrome.



Figure 5. Patient with Rabson Mendenhall Syndrome.



Figure 6. Patient with Rabson Mendenhall Syndrome.



Figure 7. Patient with Rabson Mendenhall Syndrome.



Figure 8. Patient with Rabson Mendenhall Syndrome.



Figure 9. Patient with Rabson Mendenhall Syndrome.

5. Discussion

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. These syndromes can be suspected clinically but genetic studies to confirm the diagnosis should be done [3].

Table 2. *Classification of severe insulin resistance [12].*

Aetiology	Clinical syndrome
Mutations of the insulin receptor	Donohue's syndrome (leprechaunism (Rabson–Mendenhall syndrome Type A insulin resistance
Post-binding defects in insulin action	Lipodystrophic disorders (partial or generalised; inherited or acquired (Type C insulin resistance (HAIR-AN syndrome; PCOS)
Anti-insulin receptor antibodies	Type B insulin resistance
Others	Associated with skeletal dysplasia, Alstrom syndrome, myotonic dystrophy

Rabson and Mendenhall in 1956 reported 3 siblings with dental and skin abnormalities, abdominal distension, phallic enlargement, early dentition, coarse senile faces, hirsutism, mental precocity, prognathism, thick fingernails and acanthosis nigricans [14]. 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 quantitatively normal response [3]. Severe insulin resistance in an insulin-dependent subject might be suspected when requiring more than 200 units per day insulin [13].

But this definition does not reflect the possibility that the insulin resistance can be selective and only relate to particular functions of insulin. The more appropriate definition may be that insulin resistance exists whenever normal concentrations of insulin produce less than normal biological responses described by Kahn in 1976 with respect to glucose uptake, suppression of hepatic glucose production, decreased lipolysis, increased lipogenesis and prevention of proteolysis [13].

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 level. 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) [15-17]. Type A insulin resistance syndrome and RMS have overlapping features but different clinical courses. Indeed this type is at the least severe end of the spectrum and may be also due to defect in post-receptor signaling [13]. Many of this patients paradoxically present with hypoglycemia. They have very elevated fasting insulin levels which may be sufficient to control fasting glucose levels but leads to post-prandial hypoglycemia due to mismatch between glucose and insulin [13]. This patients may have frank diabetes mellitus, virilization and polycystic vary syndrome [18]. The diagnosis encompasses in both sexes in teenage or early adulthood who are lean but have severe insulin resistance and acanthosis nigricans and also absence of insulin receptor autoantibodies [17]. These patients are likely to be at high risk of long term complications secondary to hyperglycemia but they are not predisposed to early mortality like other groups of insulin

resistance [13].

Type B insulin resistance syndrome is an autoimmune condition with anti IR antibodies being the hallmark of this syndrome [15-17, 19]. 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 in differential diagnosis of RMS, characterised by severe insulin resistance and are associated with severe hypertriglyceridemia and low HDL level [8, 15-17]. 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 [15]. They characterized by abnormalities in adipose tissue, abnormalities of carbohydrate and lipid metabolism, severe insulin resistance and immune system dysfunction. Patient's with RMS do not show raised triglycerid levels [8].

Leprechaunism presents with paradoxical fasting hypoglycemia, profound hyperinsulinemia and postprandial hyperglycemia. They have typical facial features like globular eyes, with flaring nostrils, low set ears and micrognathia. They have severe intrauterine growth retardation. Physical features typically include stunted growth and lipoatrophy. Few of these infants live beyond the first year of life, although a few may survive until adolescence. This finding have many similarities with RMS, but in RMS clinical symptoms are less severe than Donohue syndrome, and by the presence of more severe coarse feature, dysplastic dentition, gingival hyperplasia, pineal gland hyperplasia, ketoacidosis and survival beyond infancy [3, 17, 20].

Standard therapies in insulin resistance syndromes is generally supportive and the goal is maintenance of glucose in constant levels with frequent or continuous feeds and complex carbohydrates and insulin is not effective at usual doses and need to use extra-large doses of insulin (up to 9u/kg/h). 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 [17, 21, 22]. Patients with RMS have been treated with high doses of insulin and insulin sensitizing drugs [4, 5, 10, 23]. 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 [23]. 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 [21].

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 [23].

The mechanism is unclear [24-25]. One study showed that pharmacological doses of leptin in two RMS patients results in improvement of fasting hyperglycemia, hyperinsulinemia, glucose and insulin tolerance [12]. In rodent models several mechanisms could be relevant, include the activation of 5 AMP kinase which will increase insulin sensitivity also it is possible that there could be an effect on insulin receptor substrate- 2 [26-27].

Insulin, proinsulin, IGF1 and IGF2 show remarkable structural and impart sequence homology [28-29]. Receptors of insulin and IGF1 are related in structure and share common post-receptor signaling pathways [30]. 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 [31-33]. Also has been shown that rhIGF1 suppress hepatic glucose production through unknown mechanisms [34-35]. There for rhIGF1 therapy in patients with severe insulin resistance may be effective. High insulin levels acting through the IGF₁ receptors is responsible for many of the pathological features like acanthosis nigricans and polycystic ovaries [23, 36].

The aim of IGF₁ therapy is primarily stimulation utilization of peripheral glucose and suppression of hepatic glucose production and in long time aim to improve glycemia and promotion of linear growth and prolong longevity [23, 36].

Table 3. Summary design and outcome of studies on recombinant human insulin-like growth factor I (rhIGF-I) treatment in syndromes of severe insulin resistance [13].

Authors	Trial design	Outcome
Schoenle et al. [36]	Three subjects twice received i.v. doses with rhIGF-I	Immediate slow fall in blood glucose, parallel fall in insulin and C-peptide levels
Morrow et al. [37]	Two subjects received 3–4 weeks treatment with rhIGF-I. Pre- and post-treatment assessment with 24 h glucose and insulin profile, standardised liquid meal ,insulin tolerance test, insulin suppression test and i.v. glucose tolerance test	Decreased endogenous insulin levels, normalisation of response to i.v. insulin, reduced steady-state plasma glucose
Zenobi et al. [38]	Two subjects received 10 days treatment with rhIGF-I. Fasting and post-prandial glucose, insulin, C-peptide and proinsulin levels measured pre- and post-treatment	Fasting glucose levels decreased and fasting insulin, C-peptide, and proinsulin levels decreased by w65% during treatment
Kuzuya et al. [39]	11 subjects received up to 16 months treatment with rhIGF-I. Fasting and post-prandial glucose, fructosa-mine and %HbA1C were measured pre- and throughout treatment	Lowering of fasting and post-prandial glucose and decreases in fructosamine and %HbA1C
Moses et al. [40]	Six subjects (four out of six subjects had overt diabetes, two with normal glucose tolerance) received 1 months treatment with rhIGF-I. Baseline investigation to quantify carbohydrate tolerance, insulin secretion and insulin action	Three out of four diabetic subjects showed normalization of fasting and post-prandial glucose levels. Remaining two subjects dramatically decreased insulin and triglyceride levels
Vestergaard et al. [41]	Four subjects received high-dose treatment with rhIGF-I for 2 weeks, three subjects received low dose for 10 weeks. Pre- and post-treatment fasting glucose, insulin, C-peptide and proinsulin plus %HbA1C and fructosamine were measured	High-dose treatment lowered fasting glucose and insulin levels, whereas metabolic and glycaemic effects of 10 weeks low-dose treatment were modest

In early studies very high doses of rhIGF1 were used and complications were observed like muscle pain, fluid retention, benign intracranial hypertension and worsening of retinopathy [16]. A study using rhIGF1 in a patient with Donohue's syndrome reported normalization of glucose [43]. Recent studies have been able to explore the efficacy of IGF1 combined with IGF1BP3 in a variety of diabetic conditions [43-44]. This combination prolongs IGF1 half-life and result in decreased concentration of free IGF1 and improved tolerability [44-45].

An important results from there new studies was that complex therapy with IGF1/IGF1BP 3 would improve betacell function and glucose-stimulated c-peptide responses. Recent animal studies indicated that IGF1 signaling through the IGF1 receptor on the betacell may have an important role in maintaining betacell mass and insulin secretion [46-49].

This might indicate benefits of early rather than later

treatment with rhIGF1 [13].

Recombinant leptin and / or IGF-1 might provide further therapeutic options for these patients in the event of secondary treatment failure [21].

With time these patients progress to persistent hyperglycaemia and diabetic ketoacidosis. This is due to progressive decline of insulin levels, which is inadequate to prevent glucose synthesis in the liver and prevent release of fatty acid by adipocytes [23].

RMS patients have a poor prognosis, but survival is higher than 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 [24]. With the advent of newer therapies, the future holds promise for patients with RMS.

6. Conclusion

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.

An important results from there new studies was that complex therapy with IGF1 / IGF1BP3 would improve betacell function and glucose-stimulated c-peptide responses. Recent animal studies indicated that IGF1 signaling through the IGF1 receptor on the beta cell may have an important role in maintaining beta cell mass and insulin secretion [47-50]. This might indicate benefits of early rather than later treatment with rhIGF1 [13].

Therefore, careful research investigations to complete the therapeutic process are a necessity.

So early detection of the disease and controlling the symptoms of the disease is one of the priorities of supportive treatment in these patients. Providing health care to the patient And the support of companions and patient carers be a priority at the level of care because one of the most important health care in rare diseases is how to deal with the patient and choose the best treatment.

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