



Rabson–Mendenhall Syndrome with Severe Insulin Resistance Type A: The Need to Act Faster than the Disease

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Abstract

Introduction Rabson–Mendenhall syndrome (RMS) is an autosomal disorder where severe insulin resistance is observed. Insulin levels decrease over time and suppress gluconeogenesis in the liver. Fatty acid oxidation is affected, leading to frequent episodes of ketoacidosis. The changes in RMS are much faster than in patients with type 2 diabetes. RMS patients have a significantly reduced life expectancy and may die during adolescence or early adulthood.

Case Presentation A 15-year-old girl presented with poorly controlled diabetes. She was diagnosed with RMS at the age of 50 days, and her genetic study showed a homozygous mutation for R141W in the INSR gene. Her insulin level was high at 737 μ U/mL, insulinoma antigen 2 and glutamic acid decarboxylase antibodies were negative, and C-peptide was > 18 ng/mL. There is a strong family history of RMS on her mother's side. Her hyperglycemia was treated with an insulin pump (requiring up to 300 units of insulin/day) and oral rosiglitazone for the first 6 years. Rosiglitazone was replaced by oral insulin-like growth factor 1 (IGF1). Over the last 3 years, she had four further episodes of diabetic ketoacidosis triggered by infections and severe lipodystrophy. A trial of leptin and subcutaneous IGF1 has failed. The patient has a closed-loop insulin pump MiniMed 780G with a total daily dose of 261 units (4.6 U/kg/day).

Results During the past 15 years, the patient suffered many health, psychological, family, and school issues. These issues were due to RMS itself, complications of diabetes, side effects of medications, and technology failure. Our multidisciplinary team tackled all issues by providing the most appropriate care, mediation, and technology.

Conclusion To act faster than the disease progression, we need to know the whole list of issues our patient could face, as this will help us to look at the entire picture rather than treating different pieces separately. Effective cooperation between the teams is crucial and needs to be organized through a family physician or by the team involved the most in patient care. Although technology has limitations, it still helps when used appropriately.

Keywords

- insulin resistance type A
- Rabson–Mendenhall syndrome
- RMS

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Introduction

Insulin resistance is one of the most challenging conditions, and it is identified as an unexpected subnormal response to endogenous and/or exogenous insulin. Commonly, insulin resistance is diagnosed in obese patients because of the variable abnormality spectrum of glucose homeostasis, which leads to abnormal glucose metabolism.¹

Rarely severe insulin resistance is found with genetic syndromes. Abdominal obesity, particularly accompanying insulin resistance on peripheral glucose and fatty acid utilization, leads to type 2 diabetes. While in severe insulin resistance syndromes, patients usually present with hyperglycemia notwithstanding very high doses of insulin due to insulin receptor dysfunction. The insulin resistance secondary to genetic mutations shares a similar clinical picture, and patients with the genetic syndromes characteristically have intense insulin resistance along with some severe phenotypes.²

Rabson–Mendenhall syndrome (RMS) is a rare autosomal disorder marked by severe insulin resistance associated with various phenotypic manifestations. A severe insulin-resistant type of diabetes was first reported by Mendenhall in 1950; postmortem hyperplasia of the pineal gland was described in the child.³ In 1956, Rabson et al identified RMS in three children with familial hypertrophy of the pineal gland and diabetes mellitus.⁴ Later in 1975, West et al described two siblings with similar clinical features associated with dysmorphism.⁵ Patients with RMS survive early childhood but have a significantly reduced life expectancy and may die during adolescence or early adulthood. However, one case study from Spain reports on long-term survival in a patient with RMS.⁶ The changes in RMS are much faster than in patients with type 2 diabetes mellitus.⁷

Case Presentation

We report the case of a 15-year-old female with poorly controlled diabetes. The girl was presented in diabetic ketoacidosis (DKA) at the age of 50 days, and her genetic study showed a homozygous mutation for R141W in the INSR gene, known to cause RMS. A strong family history of RMS in her mother's cousins (one affected and two carriers) was noted.

She was a full-term baby, born by caesarian section with a birth weight of 2.19 kg, and required 10-day admission to the neonatal unit. She was readmitted on day 50 in DKA. Her insulin level was high at 737 μ U/mL, insulinoma antigen 2 and glutamic acid decarboxylase antibodies were negative, and C-peptide was > 18 ng/mL (5.99 nmol/L). After recovery, the patient's blood glucose level was stabilized on a very high dose (200–300 IU/day) of concentrated insulin through continuous subcutaneous insulin infusion (CSII); oral rosiglitazone was added after 2 months. This treatment was continued for 6 years, after which oral mecamermin replaced rosiglitazone.

From 6 to 12 years old, she had four further episodes of DKA associated with acute infections—right lobar pneumonia, cellulitis of the abdominal wall, acute gastroenteritis,

and lipohypertrophy, respectively. In each episode, she required high doses of intravenous insulin infusion (up to 5 IU/kg/hour). Her CSII treatment led to the development of severe lipodystrophy at the cannula insertion sites; this has led on two occasions to quick switching of her CSII to multiple daily injection therapy; glargine 300 IU daily, lispro 20 IU three times a day along with mecamermin, and SGLT2 inhibitor. Recently, she had a further two episodes of DKA precipitated by severe methicillin-resistant *Staphylococcus aureus* septicemia and unnoticed pump failure; it was managed as usual with very high doses of intravenous insulin infusion.

From 2020 to 2021, the patient was on combined therapy of mecamermin 25 units subcutaneously twice daily and oral dapagliflozin 10 mg once daily along with CSII, Medtronic 640 using insulin lispro (the total daily dose is 261 units/day (4.6U/kg/day) with insulin to carbohydrate ratio of 1:3 g, and insulin sensitivity factor of 1:20 mg/dL. A trial of recombinant human leptin was not adequate and was stopped.

Currently, she is being treated with dapagliflozin/metformin 10/1,000 mg tablet (Xigduo) and shifted to CSII hybrid closed-loop system (Medtronic 780G) to improve her glycemic control, insulin resistance, and quality of life. Despite intensified therapy, team, and family support, her glycemic control remains poor, with an average blood glucose of 304 ± 86 mg/dL and hemoglobin A1c of $10.8 \pm 1.2\%$.

Our patient's suffering started soon after birth. However, the problems list has increased and become more complicated over the last 5 years, as summarized in ►Table 1.

Discussion

Insulin resistance is one of the most serious issues RMS patients face; therefore, glycemic control is a challenging process in the management course of these patients. A mutation in the INSR gene causes severe compromise of insulin receptor (INSR) function in RMS. An interaction between insulin and insulin-like growth factor 1 (IGF1) receptors causes a noticeable delay in linear growth and failure to thrive. The patient presented with high fasting and post prandial blood glucose level despite the very high insulin; this can be explained by the improper hepatic insulin clearance or hepatic steatosis in patients with RMS due to INSR dysfunction.⁸

This patient was tried on so many medications to reduce insulin resistance, and most of the medications failed, although each time, the failure was related to the ineffectiveness of the medication. However, compliance issues could not be ruled out.

Frequent hospital visits due to multiple issues and requiring different specialties and subspecialties were a considerable burden to the family, requiring a lot of time, money, and effort. Our team tried to reduce this burden by combining five to six specialties' appointments on the same day. Pump clinic multidisciplinary team (MDT) room in where (in The Imperial College London Diabetes Centre–Abu Dhabi) the endocrinologist, dietician, diabetes educator, and psychologist sat next to each other, while the nephrologist, cardiologist, retinal camera examination,

Table 1 List of all the issues our patient has faced over the last 5 years

Issues	Year				
	2019	2020	2021	2022	2023
1. Consumption of > 200 units of insulin daily: cannula site issues, blockage, and poor insulin absorption					
2. Lack of subcutaneous fat limiting injection site area					
3. Concentrated insulin cannot be used due to the algorithm, compatibility, and safety issues					
4. Frequent set change: stress, time-consuming, and high cost					
5. Technical issues, frequent faults, and frequent alarms					
6. Alarm fatigue led to no response and poor control					
7. Pump failure led to returning to insulin injection a couple of times					
8. Sleep disturbance due to frequent alarms					
9. Puberty					
10. Menstrual periods/stress					
11. Increased time off school and school performance deterioration					
12. Psychological issues: patient getting bullied at school, developed depression, low self-esteem, and refusal to take medication					
13. Severe nonproliferative diabetic retinopathy in the left eye, nephropathy (high microalbuminuria and high albumin creatinine ratio), hypothyroidism, and celiac disease					
14. Carelessness, self-harm thoughts, and suicidal tendency					
15. Family issues and less time given to siblings, affected the work of parents					
16. Failure of some treatment options (for example IGF1 and leptin)					
17. Side effects of some medications (lactic acidosis: metformin; lipohypertrophy: insulin/cannula; worsening of the dysmorphic features: leptin)					
18. Frequent episodes of DKAs (more than five severe episodes)					
19. Frequent hospital admission (DKA, hypoglycemia, skin lesions, COVID-19, etc.)					
20. Frequent hospital outpatient visits (endocrine, nephrology, gastroenterology, psychology, psychiatry, ophthalmology, genetics, and dentistry clinics)					
21. Frequent blood testing for various reasons, with trauma due to difficulty of getting samples					
22. Family situations and issues (mother with thyroid cancer and heart problem) worsened the control					

Abbreviations: COVID-19, coronavirus disease 2019; DKA, diabetic ketoacidosis; IGF1, insulin-like growth factor 1.

and ophthalmologist were in the same building. The school nurse was contacted regularly by our diabetes educators, and issues were discussed with the patients and parents in our pump MDT clinic.

Another issue faced by our patient was the systemic development of lipohypertrophy and high consumption of pump accessories due to high insulin volume requirement. We have tried to reduce the insulin volume used by this patient (hence, reducing lipohypertrophy and consumption of pump accessories) by using concentrated insulin. However, after discussing the idea with the pump technology team, this was not possible due to safety issues, and our request was passed to the team dealing with the pump algorithm. The technology team may need to improve their pumps' algorithm to suit patients requiring concentrated insulin.

The insurance team was approached, the consumption of insulin and pump consumables was discussed, and we managed to get the approval process easier and faster. Our nurses were instructed to take extra blood samples each time we needed to do annual review blood tests, and the mother was asked to check her subsequent appointments with other specialties if any blood test was needed to avoid unnecessary frequent pricks.

Despite the initial resistance of the patient and her mother to see a psychologist, consent to refer the patient to our psychologist was obtained, and our psychologist and psychiatrist dealt with all psychological issues.

RMS patients have a significantly reduced life expectancy and may die during adolescence or early adulthood. However, increasing awareness among health care professionals and

providing the best available treatment may improve these patients' long-term survival and quality of life. The lack of a control group is the main limitation of the study. Therefore, further research on the management of RSM patients is required.

Conclusion

Although RMS is very rare, however, its management is very challenging. Life expectancy is short, with early mortality due to diabetes-related complications resulting from severe insulin resistance and poor glycemic control.

Knowing the list of the expected issues RMS patients could face helps us look at the entire issues of the patient and her family. This allows us to think ahead and act faster than the disease. Effective communication and cooperation between the teams is the key to success.

Advanced technology (like a closed-loop insulin pump) may make a difference. Patient compliance is essential when trying medications like leptin and IGF1 to improve insulin sensitivity and reduce hyperinsulinemia. Successful management of insulin resistance type A requires considering the patient's and family's situation. Further research on the management of RSM patients is required.

Patient Consent

The authors confirm that the manuscript was submitted to the journal with the patient's and her mother's permission.

Compliance with Ethical Principles

No ethical approval is required for single case reports.

Authors' Contributions

All named authors are involved in the patient's care and contributed substantially to the manuscript's conceptualization, data collection, drafting, and finalization.

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None.

Conflict of Interest

None declared.

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