Section: Pediatrics

A Case Series

GENETIC INSULIN RESISTANCE SYNDROMES - A CASE SERIES

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ABSTRACT

Background: This case series involves three pediatric patients with distinct insulin resistance syndromes, each presenting unique clinical features and genetic underpinnings. The cases highlight the importance of genetic testing, early diagnosis, and long-term management in rare metabolic disorders.

Case 1: Rabson Mendenhall Syndrome (RMS)

- **Presentation:** A 9-year-old female with a history of small for gestational age (SGA), short stature, acanthosis nigricans, hyperkeratosis, hirsutism, coarse facies, dental malocclusion, protuberant abdomen, clitoromegaly, and hyperglycemia. Notably, nephrocalcinosis was observed, adding an unexpected detail of kidney involvement.
- **Diagnosis and Management:** Diagnosis was delayed due to initial misdirection (urine mucopolysaccharides test) and loss to follow-up from age 2 to 8 years. Treatment included metformin (60 mg/kg/day) and insulin (2.5 U/kg/day), with ongoing monitoring for renal and metabolic complications.

Case 2: Heterozygous INSR Gene Mutation

- **Presentation:** A 5-year-old male with SGA, short stature, acanthosis nigricans, hyperkeratosis, hypertrichosis, but no dental malocclusion, normal male genitalia, and no hyperglycemia. However, severe hyperinsulinemia was noted, suggesting early insulin resistance.
- **Diagnosis and Management:** Early genetic testing identified the heterozygous INSR mutation, enabling diagnosis before diabetes onset. The patient requires long-term monitoring for potential future diabetes, with no current pharmacological intervention needed.

Case 3: Congenital Generalized Lipodystrophy Type 2 (CGL2)

- **Presentation:** A 4-year-old male with abdominal distension, thin limbs despite voracious appetite, tall stature, lack of subcutaneous fat, "old man" face, muscular body, massive hepatosplenomegaly, acanthosis nigricans, hyperkeratosis, rough skin, and hyperactivity. Laboratory findings confirmed hyperglycemia, hyperinsulinemia, and hepatic steatosis.
- Diagnosis and Management: Genetic testing revealed a homozygous BSCL2 mutation (c.604C>T, p.Arg202TER), confirming CGL2. Management is challenging, with metreleptin considered but cost-prohibitive. Monitoring focuses on complications like cirrhosis and cardiomyopathy, with no definitive therapy available.

INTRODUCTION

Introduction to Insulin Resistance Syndromes

Insulin resistance syndromes encompass a spectrum of rare genetic and acquired disorders characterized by defective insulin signaling or secondary adipose tissue abnormalities. These syndromes can result from primary defects, such as mutations in the insulin receptor gene (INSR), or secondary effects, such as those seen in lipodystrophies due to mutations in

genes like BSCL2. The global prevalence of these conditions is low, with congenital generalized lipodystrophy (CGL) estimated at 1 in 10 million.[7] The cases presented here illustrate the clinical diversity and diagnostic challenges, emphasizing the need for early genetic evaluation and multidisciplinary care.

Case 1: Rabson Mendenhall Syndrome (RMS) and Nephrocalcinosis

Clinical Presentation and Diagnosis: The 9-year-old female patient exhibited a classic RMS phenotype, including short stature, acanthosis nigricans, hyperkeratosis, hirsutism, coarse facies, dental malocclusion, protuberant abdomen, clitoromegaly, and hyperglycemia. An unexpected detail was the presence of nephrocalcinosis, identified via ultrasound showing bilateral bulky kidneys with medullary sponge kidney, which aligns with literature reporting nephrocalcinosis in 66.67% of RMS patients with kidney disease.[1] The diagnosis was delayed due to initial confusion with urine mucopolysaccharides (MPS) testing, which was falsely positive, and a gap in follow-up from age 2 to 8 years, attributed to parental non-compliance.

Literature Comparison: A comprehensive review of 42 RMS cases found it to be associated with Homozygous acanthosis nigricans in 69.05%, growth retardation in 59.52%, dental anomalies in 54.76%, and hirsutism in 40.48%, with mean glycosylated hemoglobin at 9.35% and fasting insulin at 349.96 µIU/mL [1]. Nephrocalcinosis, as seen in this case, is a known complication, with 85.71% of patients having kidney disease, of which 66.67% had nephrocalcinosis [1]. The homozygous INSR mutation, though not specified, is consistent with the autosomal recessive inheritance typical of RMS, caused by biallelic loss-of-function variants.[8]

Management and Outcomes: Treatment involved metformin at 60 mg/kg/day and insulin at 2.5U/kg/day, reflecting the severe insulin resistance. Long-term monitoring is crucial for managing hyperglycemia and renal complications, given the progressive nature of the disease. Achievement of normoglycemia remains a challenge in this patient, due to severe insulin resistance, despite the high dose.

Case 2: Heterozygous INSR Gene Mutation

Clinical Presentation and Diagnosis: The 5-year-old male patient presented with SGA, short stature, acanthosis nigricans, hyperkeratosis, hypertrichosis, but no dental malocclusion, normal male genitalia, and no hyperglycemia (fasting blood sugar 96 mg/dl, HbA1c 5.8%). However, severe hyperinsulinemia was evident (fasting insulin 230 mIU/L, postprandial insulin 280 mIU/L), indicating early insulin resistance. Genetic testing confirmed a heterozygous INSR mutation, enabling early diagnosis of congenital insulin resistance syndrome.

Literature Comparison: Heterozygous INSR mutations are associated with type A insulin resistance syndrome, often presenting in adolescence or early adulthood with severe insulin resistance, acanthosis nigricans, and hyperandrogenism in females.[2,3] Case reports also describe neonatal hyperinsulinemic hypoglycemia (HH) that resolves, with some family members developing diabetes later in life [4]. For instance, a case series reported patients with heterozygous INSR mutations presenting with HH in infancy, responsive to diazoxide, and later developing diabetes in adulthood [4]. The current case, at age 5, shows normoglycemia with high insulin levels, suggesting a milder phenotype that may progress to diabetes around puberty, consistent with literature findings of onset typically in adolescence.[3]

Management and Outcomes: No pharmacological intervention is currently required, but long-term monitoring is essential to detect early signs of diabetes, given the variable phenotype and potential for later metabolic deterioration.

Case 3: Congenital Generalized Lipodystrophy Type 2 (CGL2)

Clinical Presentation and Diagnosis: The 4-year-old male patient exhibited classic CGL features, including abdominal distension, thin limbs despite voracious appetite, tall stature, lack of subcutaneous fat, "old man" face, muscular body, massive hepatosplenomegaly, acanthosis nigricans, hyperkeratosis, rough skin, and hyperactivity. Laboratory findings confirmed hyperglycemia (HbA1c 7.3%, fasting blood sugar 230 mg/dl), hyperinsulinemia (fasting insulin 262 mIU/L, postprandial >300 mIU/L), elevated liver enzymes (SGOT 134 U/L, SGPT 148 U/L), and triglycerides (55mg/dl). Ultrasound revealed hepatosplenomegaly with steatohepatitis, and liver biopsy showed macrovesicular steatosis and impending cirrhosis. Genetic testing identified a homozygous BSCL2 mutation (c.604C>T, p. Arg202TER), confirming CGL2.

Literature Comparison: CGL2, caused by BSCL2 mutations, is characterized by near-total absence of adipose tissue, leading to severe metabolic complications. A review noted that 79.5% of CGL2 patients have congenital lipoatrophy, with diabetes onset common and a 15% premature mortality rate due to complications like cardiomyopathy.[5] The specific mutation c.604C>T, a nonsense mutation, has been reported with a frequency of 5.7% in BSCL2 mutations, associated with severe phenotypes [6]. Case series of CGL patients highlight hepatomegaly and hypertriglyceridemia as frequent findings, aligning with this case.[7]

Management and Outcomes: Dietary management and tab metformin 500mg OD were given. Management is challenging, with no definitive therapy available. Metreleptin (0.06–0.13 mg/kg/day subcutaneously) has been tried but is cost-prohibitive, limiting access.[7] The progressive nature of CGL2, with risks of cirrhosis, cardiomyopathy, diabetes, and dyslipidemia, underscores the poor prognosis and the need for ongoing monitoring.

Comparative Analysis and Clinical Implications

The three cases illustrate the heterogeneity of IRS, with RMS (Case 1) and CGL2 (Case 3) presenting

with severe metabolic and systemic complications, while the heterozygous INSR mutation (Case 2) shows a milder, potentially pre-diabetic state. The presence of consanguinity in all cases (5th-degree in Case 1, 3rd-degree in Cases 2 and 3) suggests autosomal recessive inheritance, a common feature in these syndromes.[1,4,5] Diagnostic delays, as seen in Case 1, highlight the need for high clinical suspicion, especially in children with failure to thrive and acanthosis nigricans.[8] Genetic testing is critical, as demonstrated by early diagnosis in Case 2, enabling tailored monitoring.[2,3]

Treatment strategies vary, with insulin sensitizers and insulin therapy partially effective in RMS, while CGL2 management remains limited by cost and availability of therapies like metreleptin.[7] The cases underscore the importance of multidisciplinary care, involving endocrinology, genetics, nutrition, and potentially cardiology and hepatology, given the multisystem involvement.[9]

RESULTS

Table 1: Comparison of Clinical Features in the Case Series and Literature

Feature	Case 1 (RMS)	Literature (RMS),[1]	Case 2 (Het INSR)	Literature (Het INSR),[2,3]	Case 3 (CGL2)	Literature (CGL2),[5]
Age at presentation	9 years	Variable	5 years	Adolescence/early adulthood	4 years	Birth/early childhood
Gender	Female	variable	male	variable	male	variable
Short stature	Yes	59.52%	Yes	Variable	No (tall)	Variable
Acanthosis nigricans	Yes	69.05%	Yes	Common	Yes	Common
Hyperkeratosis	Yes	Variable	Yes	Variable	Yes	Variable
Hirsutism/Hypertrichosis	Yes	40.48%	Yes	Common in females	Yes	Variable
Dental anomalies	Yes	54.76%	No	Not typical	No	Not typical
Genital abnormalities	Clitoromegaly	Variable	Normal	Variable	Normal genitalia	Clitorimegaly in some
Hyperglycemia	Yes	Common	No	Common	Yes	Common
Hyperinsulinemia	Yes	Common	Yes	Common	Yes	Common
Nephrocalcinosis	Yes	66.67% of kidney diseases	No	Not typical	No	Not typical
Hepatomegaly	No	Common	No	Not typical	Yes	Common
Splenomegaly	No	Not specified	No	Not typical	Yes	Common

This table facilitates a visual comparison, highlighting similarities and differences, such as the unexpected kidney involvement in RMS and the severe hepatic findings in CGL2.

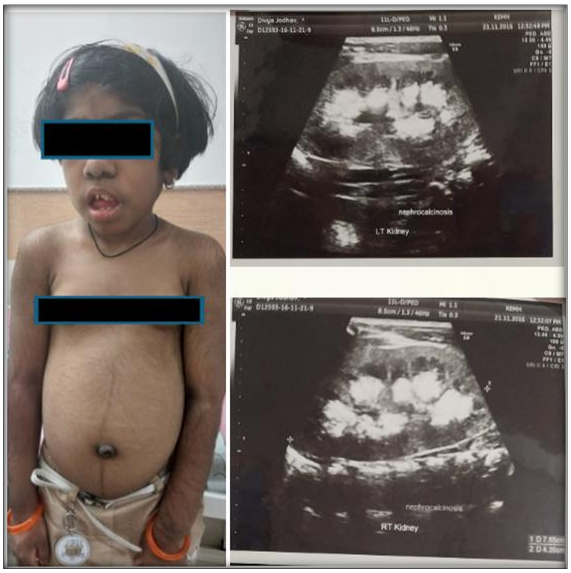

Figure 1: Hypertrichosis, Protruding abdomen are seen, USG evidence of Bilateral Nephrocalcinosis is seen. It is seen in 2/3rds of cases of Rabson Medenhall syndrome, who have homozygous insulin resistance

Figure 2: Clitoromegaly, acanthosis in skinfolds and Nape of Neck are prominent. Characteristic facies is seen, with crowding of teeth

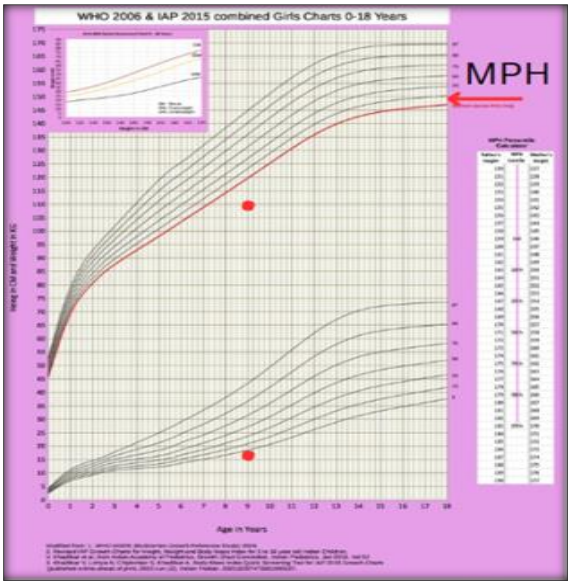

Figure 3: genetic insulin resistance syndromes result in a short stature, as opposed to insulin resistance secondary to metabolic syndrome, which cause tall stature. The underlying mechanism hasnt been studied, but could probably be due to the bone being resistant to the anabolic effect of insulin

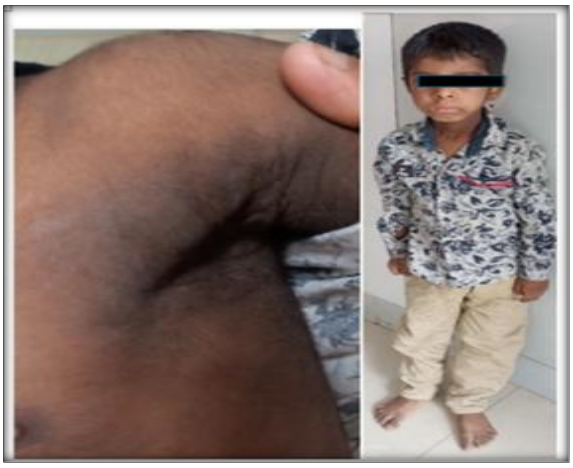

Figure 4: Acanthosis Is prominent in Axilla. Child with heterozygous genetic insulin resistance is thin built as opposed to obesity of acquired insulin resistance

Figure 5: Face is not affected much, Hypertrichosis present, dental affection is absent

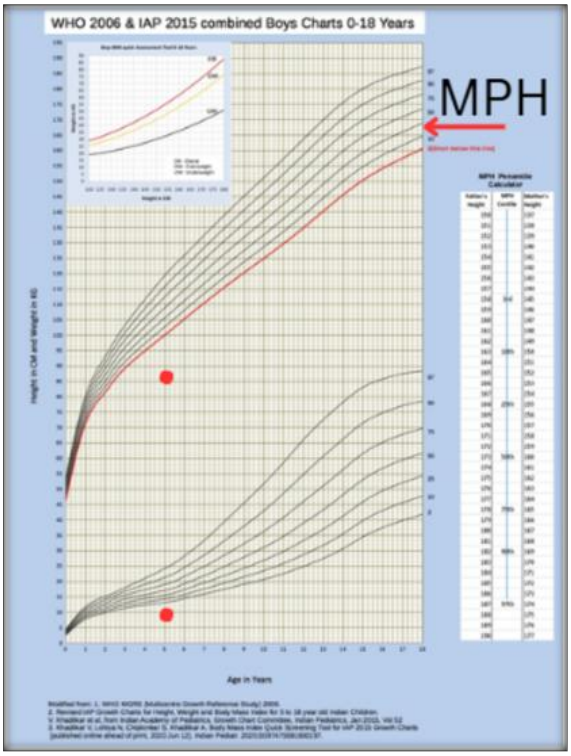

Figure 6: Heterozygous INSR gene mutations also have short stature

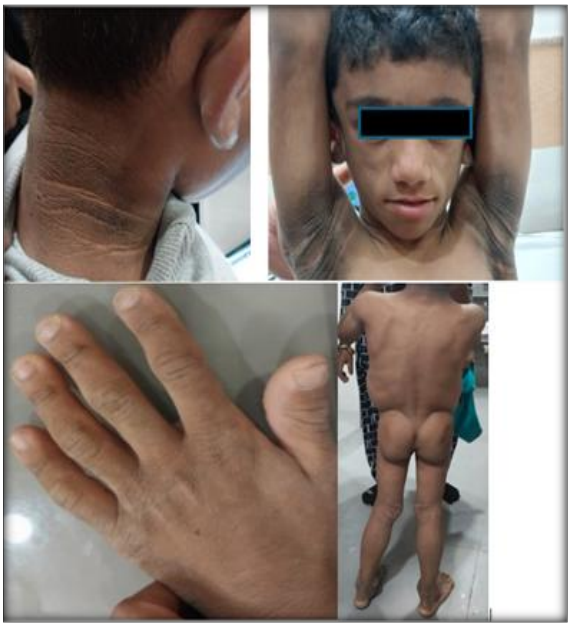

Figure 7: This child with Lipodystrophy has developed insulin resistance secondary to deposition of fat in liver. Prominent Acanthosis is seen. Very sparse subcutaneous fat in buccal area is seen- Old man appearance. Rest of the body showed sparse subcutaneous fat.

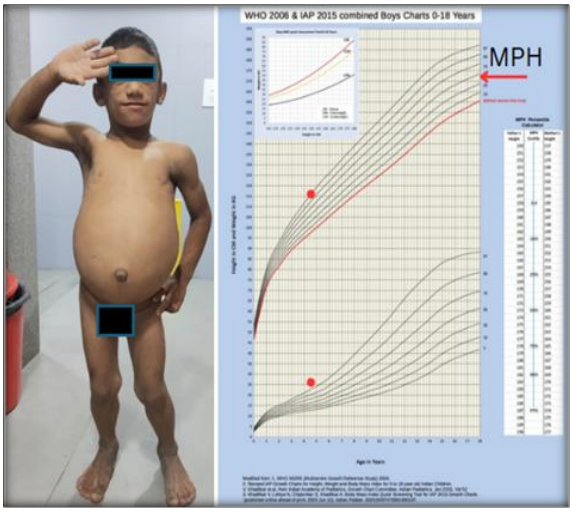

Figure 8: Abundant visceral fat and hepatomegaly was seen. Child was quite tall for his age probably due to preserved insulin sensitivity in bones

CONCLUSION

This case series emphasizes the need for a high index of suspicion in children with failure to thrive, acanthosis nigricans, and metabolic abnormalities, prompting genetic testing for accurate diagnosis. Treatment with insulin sensitizers and insulin may not always suffice, and long-term monitoring is vital for early detection and management of complications. Future research should focus on developing affordable therapies, such as metreleptin, and improving access to genetic testing to enhance outcomes in these rare disorders.

Key Citations

- Rabson-Mendenhall Syndrome: Analysis of the Clinical Characteristics and Gene Mutations in 42 Patients: https://academic.oup.com/jes/article/8/8/bvae123/7693995
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