Case Report

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Novel PIK3R1 gene mutation associated with SHORT syndrome: a case report of a 15-year-old female

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Abstract

Objectives: To present the clinical journey and management of a 15-year-old female with SHORT syndrome, highlighting the diagnostic challenges and the novel genetic mutation identified.

Case presentation: A 15-year-old Filipino female was initially seen in a dermatology clinic at 9 years old for axillary skin darkening, indicative of acanthosis nigricans. Early evaluations revealed elevated blood glucose levels, resulting in a pediatric diabetes diagnosis without the usual hyperglycemic symptoms. Her medical history was notable for premature birth, intrauterine growth restriction, a cardiac murmur from patent ductus arteriosus and a bicuspid aortic valve, delayed teething, and distinct dysmorphic features. Genetic testing identified a novel PIK3R1 gene mutation. Treatment with Metformin significantly improved her glycemic control and lipid profiles. The patient also displayed delayed puberty and polycystic ovary syndrome-like symptoms, but growth hormone deficiency was excluded. Endocrine evaluation for her short stature and lipodystrophy confirmed the presence of the PIK3R1 mutation.

Conclusions: This case highlights the importance of thorough endocrine and genetic evaluations in patients with complex clinical presentations like SHORT syndrome. The identification of a novel PIK3R1 gene mutation expands the understanding of the genetic basis of this syndrome and underscores the need for individualized treatment approaches.

Keywords: lipodystrophy; insulin resistance; PIK3R1 mutation

Introduction

SHORT syndrome is a rare genetic disorder characterized by short stature, hyperextensibility of joints, ocular depression, Rieger anomaly, and teething delay. The syndrome presents a complex clinical picture due to its varied symptoms and genetic heterogeneity. Understanding and diagnosing this condition can be particularly challenging, especially in the pediatric population where symptoms can overlap with other common pediatric endocrine and metabolic disorders.

Case description

We present the case of a 15-year-old female of Filipino origin diagnosed with SHORT syndrome, whose clinical journey started at our clinic when she was 9 years old. The patient's initial presentation to the dermatology clinic was prompted by observed darkening of the axillary region, consistent with acanthosis nigricans. Subsequent evaluation revealed a random blood glucose level of 13.8 mmol/L, leading to a referral to our pediatric diabetes clinic. The confirmed diagnosis of diabetes was accompanied by an initial hemoglobin A1c of 8.3 %. Notably, the patient denied classical symptoms of hyperglycemia, such as polyuria, polydipsia, nocturia, or weight loss.

The patient's medical history unveiled significant details, including premature birth at 35 weeks with severe intrauterine growth restriction (IUGR) and a birth weight of 1.9 kg. A one-month stay in the NICU followed. At 6 months of age, the patient was diagnosed with a cardiac murmur secondary to patent ductus arteriosus (PDA) and a bicuspid aortic valve, necessitating ongoing cardiologist follow-up. Delayed teething, with the first tooth erupting at 19 months, and subtle dysmorphic features noted on the initial visit

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included upward slanting palpebral fissures, low subcutaneous fat which is partial, more prominent in the face, arms and thighs, underweight status for both weight and BMI, triangular face, and ocular depression. She was also below the 2nd percentile for height on initial presentation with a mid-parental height, 147.5 cm which is between the second and the 9th percentile. Thelarche initiation was observed during the examination. No hyper extensibility of joints, hernias, Rieger anomaly were noticed. Family history includes a maternal grandmother with adult-onset type 2 diabetes and similar physical features to our patient, though she has not undergone genetic testing for SHORT syndrome. The patient's mother does not exhibit dysglycemia or phenotypes associated with SHORT syndrome. Past medical history, especially concerning infections, the patient did not experience an increased frequency of infections compared to other children her age. The patient did not exhibit intellectual disability or developmental delays in mental or motor skills. Of note, her delayed teething continued to be 2–3 years behind her peers however achieved full set of permanent teeth by age of 15 years.

Further investigations revealed a normal karyotype (46XX), elevated C-peptide, 5.2 nmol/L (0.37–1.47), negative pancreatic autoantibodies GAD-65 and IA-2 antibodies, and normal leptin levels, 8.5 ng/dL (reference: 0.6–3.9 for BMI 14–15 kg/m^2). The initiation of Metformin at 500 mg resulted in a rapid improvement in glycemic control, with hemoglobin A1c reaching 5.3 % within three months. Lipid panel measurements included initial LDL of 2.2 mmol/L with a peak of 3.1 mmol/L (0–2.56), initial triglycerides of 1.1 mmol/L with a peak of 2.92 mmol/L(0–1.01), and marginally elevated ALT, 32 u/L and AST, 31 u/L levels (0–24). Remarkably, insulin levels were markedly elevated at 393 pmol/L (18–173). Complete blood count was essentially normal showing a white blood cell count=8.59 ˆ9/L (3.7–10.5) with differential count within normal range: neutrophils=5.3 (1.5–5.6), lymphocytes=2.26 (1.1–3.1) and monocytes=0.52 (0.1–0.7). Hemoglobin=135 g/L (117–157) and red blood cells also normal=4.71 ˆ12/L (3.9–5.45). Red blood cells indices were all normal. Platelet count was mildly elevated at 480 ˆ9/L (176–407) however on repeat evaluation it normalized. Electrolytes including sodium and potassium were normal as well as kidney functions including urea=4.5 mmol/L (1.8–6.4) and creatinine=52 μmol/L (50–88). Her albumin level was normal=52.9 g/L (35–55).

Throughout clinic follow-ups, glycemic control remained stable, with hemoglobin A1c ranging between 5.3 and 7.6 %. Metformin dosage was eventually increased to 500 mg twice daily. Her linear growth seems to have improved after initiating treatment until she was about 10 years of age. Normal breast development progressed to Tanner IV, with no menarche observed. Due to delayed puberty and hirsutism, hormonal profiling revealed PCOS-like abnormalities most likely related to her insulin resistance showing mildly elevated LH, 17.04 iu/L (0.5–41.7), FSH, 11.47 iu/L (1.66–17) with normal estradiol, 171 pmol/L (46–609) and mild hyperandrogenism including mildly elevated testosterone, 4.5 nmol/L, mildly elevated androstenedione, 3.36 ng/mL (0.1–2.1) with normal 17 hydroxyprogesterone, 138 ng/dL (18–230) making late onset CAH unlikely. ACTH, cortisol as well as prolactin were normal. A pelvic ultrasound showed a normal endometrium measuring 4.9 mm.

Pediatric endocrinology evaluation, prompted by short stature concerns, revealed normal IGF-I, 459 ng/mL (146–480), IGFBP-3, 4,641 μg/mL (2,580–6,365) and a glucagon stimulation test with a peak growth hormone of 7.89 ng/mL ruling out growth hormone deficiency. Bone age consistent with 15 years and completely fused epiphysis indicated that growth hormone therapy was not indicated. Referral to our endocrine geneticist was made due to dysmorphic features, lipodystrophy, severe insulin resistance and history of IUGR. Whole exome sequencing identified a heterozygous mutation in the PIK3R1, c.1968del, p.(Tyr657Metfs5), heterozygous, likely pathogenic. The variant is located on the penultimate exon and disrupts the last 69 amino acids, including the SH2 domain. Therefore, this variant is expected to affect the protein function. This variant is absent in the general population from gnomAD. This variant has not been reported in individuals with PIK3R1-related phenotypes in the literature.

Discussion

The case presented herein aligns with the classification of a Genetic insulin resistance syndrome, commonly known by the acronym SHORT syndrome [1]. The nomenclature stems from its characteristic features: short stature (S), hyperextensibility of joints, and/or inguinal hernia (H), ocular depression (O), Rieger anomaly (R), and teething delay (T) [2]. Notably, the acronym SHORT does not explicitly encompass lipodystrophy or insulin resistance, which, intriguingly, are consistent features in the majority of reported cases. Mutations in PIK3R1 result in the loss of function or reduced activity of the PI3K complex, leading to impaired activation of the AKT pathway. This disruption affects cellular processes like growth, metabolism, and survival, contributing to the clinical features of Short syndrome, such as growth retardation, lipodystrophy, and insulin resistance. This has been shown in functional analysis in fibroblasts [2].

Our patient exhibited a unique manifestation, encompassing intrauterine growth restriction (IUGR), teething delay,

insulin resistance progressing to type 2 diabetes, lipodystrophy, short stature, and ocular depression. Notably, hyperextensibility of joints, hernias, and Rieger anomaly were absent. Whole exome sequencing revealed a heterozygous mutation in the PIK3R1 gene (c.1968del, p.(Tyr657Metfs*5)), a variant not previously reported in individuals with PIK3R1-related phenotypes in the existing literature.

Previous documented cases elucidated classical features, including short stature, hyperextensibility of joints and/or inguinal hernia, ocular depression, Rieger anomaly, and teething delay [2]. The impact of PIK3R1 mutation on iris development and its role in anterior segment dysgenesis, particularly Rieger anomaly, has been established in both mice and humans [3]. Dental manifestations such as teething delay, microdontia, hypodontia, and enamel hypoplasia were also reported [4].

Metabolic features associated with SHORT syndrome encompass insulin resistance, reduced lipogenesis, partial lipodystrophy, increased energy expenditure, and potential IGF1 resistance [5]. Interestingly, some cases revealed no insulin resistance or diabetes [6]. Discerning the relationship between insulin resistance and the absence of fatty liver or metabolic dyslipidemia in individuals with SHORT syndrome caused by C-terminal PIK3R1 mutations suggested that the observed lipodystrophy may be linked to increased energy expenditure rather than constituting true lipodystrophy [7].

The reported comorbidities in SHORT syndrome are diverse. Cases have documented transient neonatal diabetes mellitus [8], microcephaly, severe developmental delay or intellectual disability [9], unilateral basal ganglia calcification [10], deviated nasal septum, cryptorchidism [11], hypercalcemia, nephrocalcinosis [12], bilateral symmetrical lens opacities [13], and diffuse thyroid disease [14].

Phenotypic overlap has been observed with activated PI3K δ syndrome (APDS2) and other intrauterine growth restriction syndromes [15].

In conclusion, this case adds to the evolving spectrum of phenotypic presentations associated with SHORT syndrome, highlighting the importance of comprehensive genetic analyses in elucidating novel mutations. The observed phenotypic diversity underscores the need for a multidisciplinary approach to diagnosis and management, considering potential comorbidities and overlapping syndromes.

Learning points

- Highlights the clinical variability and presentation of SHORT syndrome in females affected by it.
- Emphasizes the importance of genetic testing in diagnosing rare syndromes with overlapping phenotypes.

What's new?

- First report of a novel PIK3R1 gene mutation linked to SHORT syndrome.
- Unique clinical findings and presentation in a 15-year-old female, contributing to the phenotypic spectrum.

Research ethics: The local Institutional Review Board deemed the study exempt from review.
Informed consent: Informed consent was obtained from all individuals included in this study. Informed consent available upon request.
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