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Case Report

Costello Syndrome: A Case Report and Literature Review

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ABSTRACT

We present the case of an 8-month-old male infant referred for poor weight gain, with a history of intrauterine growth restriction (birth weight: 2,230 g; height: 45 cm). Physical examination revealed dysmorphic features, including a broad forehead, depressed nasal bridge and low-set ears. Karyotype was 46, XY. Given suspicion of endocrine involvement, a dynamic growth hormone (GH) test with glucagon was performed and showed a peak GH level 3.5 ng/mL, consistent with GH deficiency. Trio whole-exome sequencing identified a heterozygous pathogenic variant in the HRAS gene, confirming the diagnosis of Costello syndrome. This case highlights the importance of considering syndromic etiologies and the RAS/MAPK pathway in infants with failure to thrive, as well as integrating endocrine and genetic evaluations to enable timely diagnosis.

Keywords: Costello syndrome; HRAS; RASopathy; Growth hormone deficiency

Introduction

Costello syndrome (CS) is a rare, complex, multisystem RASopathy caused by pathogenic germline variants in the HRAS oncogene. First described by Dr. J.M. Costello, it is characterized by postnatal growth failure, coarse facial features, intellectual disability and a marked predisposition to benign and malignant neoplasms[1]. The estimated prevalence ranges from 1:230,000 in Japan to 1:380,000 in the United Kingdom[2], underscoring its rarity and the challenge it poses for public health and precision medicine. Costello syndrome (CS, OMIM 218040) is the only RASopathy definitively caused exclusively by gain-of-function variants in HRAS, located on chromosome 11p15.5, which encodes a small GTPase in the RAS/MAPK signaling pathway[3]. This pathway is essential for regulating cell proliferation, differentiation and survival; dysregulation can lead to multisystem manifestations due to the ubiquitous expression of HRAS.

Most cases arise from de novo mutations and are strongly associated with advanced paternal age, suggesting a selective advantage of certain HRAS variants in male germ cells[4]. Diagnosis is confirmed by identifying a heterozygous pathogenic variant, with the p.Gly12Ser substitution accounting for approximately 80% of cases[5].

Clinical Case

An 8-month-old male infant, born to non-consanguineous parents with no known genetic diseases, was referred to paediatric endocrinology for evaluation of growth impairment. The pregnancy was described as uncomplicated; however, prenatal ultrasound noted short long bones. Delivery was by caesarean section. Birth weight and length were 2,230 g and 45 cm, respectively. No neonatal complications were documented; however, recurrent vomiting, hypotonia and feeding difficulties led to gastrostomy placement at 1 month of age. At presentation (8 months), weight was 6.2 kg (weight-for-age Z-score −2.99 SD), length was 62.7 cm (length-for-age Z-score −3.61 SD). Physical examination showed a distinctive facial appearance with a broad forehead, depressed nasal bridge and low-set ears. Limb disproportion was noted, with ligamentous laxity and elbow hypermobility. The testes were not palpable in the scrotum. The skin was loose with redundancy, especially over the neck, hands and feet, with hyperkeratosis and palmoplantar hyperpigmentation and calluses. Deep palmar and plantar creases were present.

Evaluation for common endocrine causes of growth impairment showed: TSH 2.2 mIU/L and free T4 1.1 ng/dL; morning basal cortisol 8.6 µg/dL; and low IGF-1 at 15.4 ng/dL. A glucagon stimulation test documented a low peak GH level of 3.5 ng/mL, consistent with growth hormone deficiency. Karyotype was 46, XY. Given concern for a syndromic condition versus musculoskeletal dysplasia, a skeletal dysplasia gene panel (40 genes) was initially performed and did not explain the phenotype. Due to persistent clinical suspicion, trio whole-exome sequencing was obtained and identified a pathogenic de novo heterozygous HRAS variant, c.34G>A (p.Gly12Ser), consistent with Costello syndrome (autosomal dominant). This variant was judged to explain the patient's phenotype.

Discussion

The molecular basis of Costello syndrome is germline pathogenic variants in HRAS, that result in constitutive activation or altered regulation, disrupting signalling kinetics[6]. Variants affecting codons 12 and 13 account for more than 95% of reported cases[7]. These residues are critical for the GTPbinding domain; substitutions impair efficient hydrolysis of GTP to GDP, blocking the protein in an activated ("on") state[7]. The p.Gly12Ser variant is associated with the classic phenotype of Costello syndrome[8]. However, less common variants have been associated with distinct clinical courses. From an endocrine perspective, growth hormone deficiency has been reported in 30-50% of patients. GH replacement therapy remains controversial: although it may improve linear growth velocity, there is concern given the mitogenic properties of GH and the theoretical potential to exacerbate hypertrophic cardiomyopathy or promote tumor development[5]. Available data have not demonstrated a definitive causal link between GH therapy and cancer in CS; however, close cardiac surveillance is recommended, including echocardiographic monitoring every 6 months during the first year after treatment initiation. Pubertal development is often delayed, potentially related in part to the low body fat mass characteristic of this syndrome. A 2023 meta-analysis by AstiazaranSymonds, et al. reported a cumulative cancer risk of approximately 13-15% by age 20. The most common malignancy is embryonal rhabdomyosarcoma, followed by transitional cell carcinoma of the bladder and neuroblastoma[5].

Conclusions

Costello syndrome is a complex condition entity that requires lifelong surveillance. Understanding the genotype-phenotype correlations is essential for prognosis and for tailoring cancer surveillance strategies. Rigorous multidisciplinary follow-up remains central to reducing complications and optimizing outcomes in affected individuals.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Ethical Approval

Written informed consent was obtained from the patient's legal guardians for publication. Patient identity has been anonymized.

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