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Case Report

A novel case of homozygous PAX1 mutation associated with hypoparathyroidism

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***Abstract*:** The PAX1 gene plays an important role in the development of the parathyroid glands and the thymus. Mouse knockout models of PAX1, PAX3, and PAX9 have been found to have hypoplastic or absent parathyroid glands. To our knowledge, there are no reported cases of PAX1-associated hypoparathyroidism in humans. We present a case of hypoparathyroidism in a 23-month-old boy with a homozygous pathogenic variant in the PAX1 gene (*PAX1* NM_006192.5 c.463_465del variant), predicted to cause an in-frame deletion of asparagine at position 155 (p.Asn155del) of the PAX1 protein. The hypoparathyroidism was unmasked after the patient developed significant hypocalcemia while receiving GoLYTELY (polyethylene glycol 3350, sodium sulfate anhydrous, sodium bicarbonate, sodium chloride, potassium chloride) for bowel cleanout. The patient had mild and asymptomatic hypocalcemia prior to hospitalization. The patient was noted to have inappropriately normal parathyroid hormone (PTH) level at the time of documented hypocalcemia thereby suggesting a diagnosis of hypoparathyroidism.

Plain language summary

The first human case of hypoparathyroidism associated with a rare genetic disorder: a case report of PAX1 gene mutation

The paired box (*PAX*) gene family is important for embryo development. One subfamily, PAX1, is necessary for development of the spinal column, thymus (important for the immune system development), and parathyroid (helps regulate the amount of calcium in the body). We present the case of a 23-month-old boy with known PAX1 gene mutation who came in with episodes of vomiting and poor growth. His presentation was thought to be most likely related to constipation. He was started on bowel cleanout medication and intravenous fluids. However, his calcium that had been mildly low subsequently dropped to very low levels. The level of parathyroid hormone (which helps regulate calcium levels) was inappropriately normal, meaning that his body was unable to make more, and was consistent with hypoparathyroidism. He was treated with calcium supplements and vitamin D and calcium levels normalized. He continues to be on calcium and vitamin D and calcium levels have remained stable. Doctors should keep this complication in mind when treating patients with PAX1 gene mutation.

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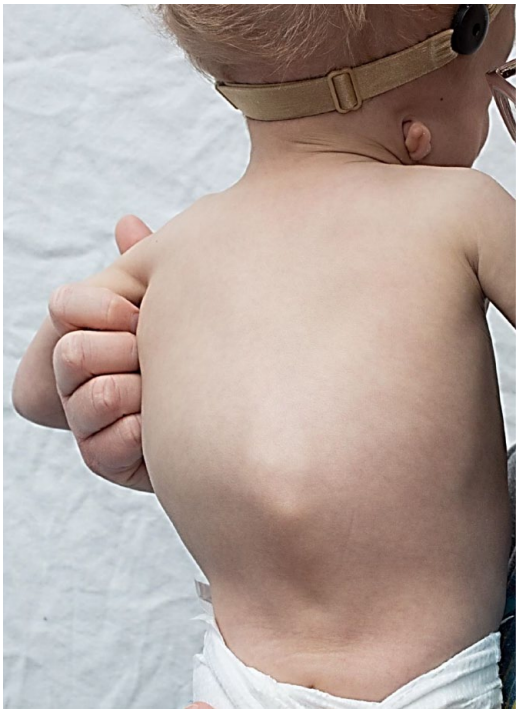

Figure 1. Photograph showing the patient standing. Anterior–posterior thoracolumbar spine shows thoracolumbar kyphosis and scoliosis with notable right-side low-set pinna and microtia.

Introduction

The paired box (*PAX*) gene family encodes transcription factors that are important for pattern formation during vertebrate embryogenesis.[1] There are nine known mouse and human PAX genes; these are classified into four subfamilies (Pax1 and Pax9; Pax2, Pax5, and Pax8; Pax3 and Pax7; Pax4 and Pax6).[2] Haploinsufficiency is the pathogenic mechanism for PAX-associated developmental defects.[3] Human PAX1 maps to chromosome 20p11.22; trisomy and monosomy of this locus are associated with vertebral anomalies.[2–4] PAX1 is necessary for axial vertebral column formation, as well as thymus and parathyroid gland development.[4,5]

Otofaciocervical syndrome 2 (OFCS2) (OMIM #615560) is a single-gene disorder with both autosomal dominant and recessive forms. Pathogenic variants in PAX1 are known to be causative for the autosomal recessive form of OFCS2.[1,5–7] OFCS2 is phenotypically characterized by facial anomalies, cup-shaped low-set ears, preauricular fistulas, hearing loss, branched defects, skeletal anomalies including vertebral defects, low-set clavicles, winged scapulae, sloping shoulders, and mild intellectual disability.

The role for pathogenic PAX1 variants in thymus development and immunodeficiency is well established.[6,8] Mouse knockout models of PAX1, PAX3, and PAX9 have hypoplastic or absent parathyroid glands.[9–14] Transcription factors that determine parathyroid development are critical for parathyroid hormone (PTH) expression. Based on its role as a transcription factor required for parathyroid gland development,[9–14] it is expected that pathogenic variants in PAX1 will result in both hypoplasia of the parathyroid gland and dysregulated parathyroid cell proliferation. To our knowledge, there are no human reported cases of hypoparathyroidism with PAX1 gene mutation.[1,11] In humans, mRNA and protein expression of PAX1 was noted to be significantly reduced in parathyroid adenomas.[15]

We describe a 23-month-old boy with homozygous pathogenic variant in the PAX1 gene who presented with hypoparathyroidism during an inpatient hospitalization for constipation and vomiting. The authors followed the CARE guidelines when preparing this article.

Case report

The patient is a 23-month-old boy who presented with 1 month of increasing emesis and poor feeding in the context of poor weight gain over a 4-month period.

He was born at term via uncomplicated vaginal delivery to non-consanguineous parents. Birth weight and length were 3.44 kg and 53.3 cm, respectively. Apgar scores were 7 and 1 at 1 and 5 min, respectively. At birth, he was noted to have distinctive and dysmorphic features (low-set pinna, microtia, receding chin, and prominent nasal bridge) with an almost identical clinical phenotype to his older 9-year-old brother, who had been diagnosed with PAX1-associated OFCS2. Physical examination was notable for thoracolumbar kyphosis and scoliosis with notable right-side low-set pinna and microtia (Figure 1). He underwent DNA sequence analysis, which showed a homozygous pathogenic variant in the PAX1 gene, *PAX1* NM_006192.5 c.463_465del variant, predicted to cause an in-frame deletion of asparagine at position 155 (p.Asn155del) of the

PAX1 protein. Of note, the older brother had the same pathogenic variant as the patient. The patient also had hydrocephalus, kyphosis, and severe syndromic immunodeficiency (complete IgA deficiency, absent T lymphocytes, low B cells, and normal natural killer (NK) cell counts with absent recent thymic emigrants indicating thymic aplasia). He was started on antimicrobial prophylaxis soon after birth with monthly intravenous immunoglobulin and pentamidine, daily fluconazole, and weekly azithromycin.

The patient's emesis was non-bloody and non-bilious and was exacerbated with pushing oral intake and medication administration. On physical examination, several dysmorphic features were noted including microretrognathia-mandibular hypoplasia, simple-cupped malformed ears bilaterally with microtia, preauricular fistulas bilaterally, hypertelorism, and downslanting palpebral fissures. He also had mixed sensorineural and conductive hearing loss. An upper esophagogastroduodenoscopy with small-bowel follow-through was normal. Head computed tomography (CT) showed stable ventriculomegaly from previous imaging without evidence of basal ganglia calcification. He was noted to have hepatosplenomegaly and bowel distention on examination. An ultrasound of the abdomen was unrevealing and showed no evidence of kidney stones or soft tissue calcification. Initial laboratory workup at the time of admission showed mild hypocalcemia (8.3 mg/dl; reference range 9.3–10.6) and normal albumin (4.3 g/dl, reference range 3.5-5.0), but was otherwise unremarkable. Previous calcium levels had been normal/borderline low and had ranged between 8.1 and 10.2 mg/dl without any reported symptoms. He had known autoimmune thyroiditis with positive thyroid peroxidase antibodies but normal thyroid-stimulating hormone (TSH).

The patient's episodes of recurrent emesis were determined to be related to constipation. He was started on bowel cleanout with GoLYTELY (polyethylene glycol 3350, sodium sulfate anhydrous, sodium bicarbonate, sodium chloride, potassium chloride), which was performed over 4 days. Interval labs during this time revealed decreasing calcium from 7.7 to 6.5 mg/dl to a critically low nadir of 5.9 mg/dl. Albumin was normal at 4.3 g/dl (reference range 3.5–5.0). Magnesium was normal at 1.9 mg/dl (reference range 1.6–2.7). PTH was inappropriately normal at 25 pg/ml (reference range 11–59), with concurrent total calcium of 6.5 mg/dl and phosphorus of 4.3 mg/dl (reference range 3.4–5.4 mg/dl). A repeat PTH level 24 h later was again inappropriately normal at 23 pg/ml with concurrent total calcium of 5.9 mg/dl and phosphorus of 3.7 mg/dl. Total 25-hydroxy vitamin D total was normal at 37 ng/ml (reference range 20–50), and 1,25 dihydroxy-vitamin D was normal at 38 pg/ml (reference range l. 24–86). The findings of inappropriately normal PTH with concurrent hypocalcemia were consistent with hypoparathyroidism.

He was started on calcium carbonate (maximum dose of elemental calcium was 100 mg/kg/day) and calcitriol (0.25 μg once daily). Initially, there was rapid improvement in the total calcium from 5.1 to 9.1 mg/dl over a 24-h period following discontinuation of GoLYTELY, but the total calcium and ionized calcium decreased subsequently (total calcium 8 to 8.6 mg/dl and ionized calcium 4.1 to 4.3 mg/dl) and therefore calcium carbonate and calcitriol were continued. Phosphorous increased to 4.6 following treatment. The timeline of significant drop in calcium level coincided with the administration of GoLYTELY and intravenous hydration with normal saline; this suggests that the bowel cleanout and intravenous hydration unmasked the patient's underlying hypoparathyroidism. Following bowel cleanout, feeds were initiated via nasogastric tube with subsequent gastrostomy tube placement. He was discharged home with calcitriol (0.25 μg once daily) and calcium carbonate supplementation (elemental calcium 75 mg/kg/day in three divided doses). He has since then needed an increase in the dose of calcium carbonate (elemental calcium 90 mg/kg/day in three divided doses) and calcitriol (0.5 μg once daily).

Discussion

To our knowledge, this is the first human case of PAX1 mutation–associated hypoparathyroidism.[1,16] Previously, hypoplastic parathyroid glands have been reported in mouse knockout models of PAX1.[17] Our case also highlights the lack of genotype and phenotype correlation with variable expressivity in children with PAX1 deficiency as the patient's brother had not shown any evidence of hypoparathyroidism by 9 years of age.

The PTH regulates serum calcium levels via its direct effect in the bone and kidneys. PTH increases serum calcium level by stimulating skeletal release via bone resorption and by promoting renal calcium reabsorption of calcium. In addition, PTH stimulates production of 1,25 dihydroxy vitamin D, the active metabolite of vitamin D that enhances the absorption of calcium in the small intestine. Hypoparathyroidism is diagnosed in the presence of hypocalcemia with a concurrent low or inappropriately normal PTH level.[18–20] While our patient had inappropriately normal PTH levels, it should be noted that the labs were not interrogated for the presence of interfering antibodies (such as heterophile and human anti-animal antibodies). Therefore, there is a possibility that the normal PTH level may be due to an unrecognized interfering antibody falsely elevating the PTH levels, and the true PTH levels were, in fact, quite low.

Hypoparathyroidism can be a consequence of abnormal parathyroid gland development due to genetic defects in any of the transcription factors related to parathyroid gland development.[17] Therefore, calcium levels should be monitored in patients with any known defects in these genes. Hypoparathyroidism should be suspected in patients who are incidentally noted to have a low serum calcium. Symptoms of hypocalcemia may include cramps, tetany, paresthesias, perioral numbness, and seizures. However, many patients may be asymptomatic. It is important to note that some patients with hypoparathyroidism may have normal calcium and phosphorus levels when they are well, but levels may decrease significantly during an intercurrent illness, during a hospitalization, or after surgery. As with our patient, calcium levels had mildly low/normal prior to this hospitalization.

Our patient had a significant decrease in calcium levels that coincided with use of polyethylene glycol–based bowel cleanout. Hypocalcemia has been described with use of polyethylene glycol–based and sodium phosphate-based lavage solutions.[21,22]

Our case emphasizes the potential and risk of hypocalcemia due to electrolyte shifts with bowel cleanout regimens. As constipation is one of the most common problems encountered in the pediatric practice,[23] this report highlights the need for caregivers to familiarize themselves with the side effects of commonly used bowel regimen medications and be able to counsel patients and their caregivers accordingly.

Initial management of hypocalcemia secondary to hypoparathyroidism focuses on treatment of symptoms and calcium repletion to the low-normal range (around 9 mg/dl). Management includes calcium supplementation, and some patients may need calcitriol. It is important to note that the major adverse effects of calcium supplementation in patients with hypoparathyroidism can include hypercalciuria, nephrolithiasis, and renal failure,[20] and therefore monitoring of urinary and serum calcium and phosphate is recommended following normalization of calcium levels.[24]

Conclusion

In summary, providers caring for children and adults with PAX-1 mutation should be aware of hypoparathyroidism as a potential clinical feature and calcium levels should be checked in these children routinely and during intercurrent illnesses, hospitalizations, and with bowel clean out even when baseline calcium levels have been normal.

Declarations

Ethics approval and consent to participate

Ethics approval is not applicable due to institutional/IRB policy for single case reports. Written informed consent was obtained from the patient's parents for treatment.

Consent for publication

Verbal informed consent was obtained from the patient's parents for publication of this case report and the images included. Verbal informed consent was obtained, as this is the standard policy approved by the Mayo Clinic Institutional Review Board for single case reports.

Author contributions

Benjamin L. Hamel: Formal analysis; Writing – original draft; Writing – review & editing.

Seema Kumar: Conceptualization; Writing – original draft; Writing – review & editing.

Leah Heidenreich: Writing – original draft; Writing – review & editing.

Avni Joshi: Data curation; Writing – review & editing.

Christiana DaSilva: Investigation; Project administration; Writing – original draft; Writing – review & editing.

Faizal Z. Asumda: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supplemental material

Supplemental material for this article is available online.

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