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Thrombocytosis in an infant with a *TRPV4* mutation: a case report

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Abstract

Mutations in the calcium channel gene *Transient Receptor Potential cation channel subfamily V member 4* (*TRPV4*) cause autosomal dominant skeletal dysplasia, with phenotypes ranging from mild to perinatal lethality. A recent report detailed enhanced proplatelet formation and increased murine platelet count in the context of *TRPV4* activation. No prior reports have described platelet count abnormalities in human *TRPV4* disease. Here, we report a case of prolonged thrombocytosis in the context of *TRPV4*-associated metatropic dysplasia that was lethal in the infantile period.

Keywords

thrombocytosis; skeletal dysplasia; TRPV4; calcium channel

Introduction

Mutations in *TRPV4* (*Transient Receptor Potential cation channel subfamily V member 4*) cause a clinically heterogenous metatropic skeletal dysplasia with autosomal dominant inheritance.[1,2] Metatropic dysplasia is characterized by short extremities, short trunk, progressive kyphoscoliosis, and distinct craniofacial abnormalities. Phenotypic severity ranges from mild to perinatal lethal, with death typically due to thoracic insufficiency.[1,2] Skeletal manifestations arise from altered TRPV4 calcium sensing and perturbed chondrocyte differentiation.[2]

In a cellular model, pharmacologic TRPV4 activation enhanced proplatelet formation.[3] *In vivo*, decreasing extracellular matrix stiffness led to increased TRPV4 activation and

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Contributions

CST, EB, and MPL interpreted data and contributed to writing this manuscript.

Disclosures of interest

The authors declare no relevant conflicts of interest.

Consent

The patient's family has given written consent to the inclusion of material pertaining to the patient's case. They acknowledge that they cannot be identified via the paper, as the patient has been fully anonymized in this manuscript. The Children's Hospital of Philadelphia Institutional Review Board deemed this study exempt from oversight.

increased platelet count.[3] To our knowledge, no prior reports have described altered platelet counts in humans with metatropic dysplasia.

Here, we report a case of *TRPV4* mutation with lethality around 4 months of age. The infant had lifelong thrombocytosis without known associated clinical complications directly related to the platelet count. This is the first report of thrombocytosis in human *TRPV4*-associated metatropic dysplasia. Thrombocytosis might be also observed in similar clinical cases.

Case

Prenatal testing for the female patient was consistent with arthrogryposis, including decreased thoracic circumference, spinal segmentation anomalies, thoracolumbar kyphoscoliosis, lumbosacral lordosis, and a tethered spinal cord. Upper and lower extremities were noted to have shortened long bones with concerns for contracture, with lower extremities more severely affected. MRI showed no significant structural anomalies of the brain or spine.

The patient was born at 32 weeks 1 day gestation by cesarean section, in the setting of prolonged premature rupture of membranes and recurrent fetal decelerations. She was admitted to our Level 4 neonatal and infant intensive care unit for respiratory support and multidisciplinary evaluation. Her clinical exam was consistent with the described prenatal imaging findings. Clinical exome sequencing identified a heterozygous *de novo* variant in *TRPV4* (c.1303 G>A, p.E435K). This mutation was not previously reported in the ClinVar or Human Mutation Gene Database registries, but was deemed a ‘likely pathogenic variant’ per ACMG guidelines.[4] Scores from *in silico* prediction tools indicated potential pathogenicity for this mutation (Supplemental Table 1).

The patient required non-invasive support via continuous positive airway pressure (CPAP), bilevel positive airway pressure (BIPAP) or high flow nasal cannula for her entire life. She was intubated in the setting of procedures, including a laparoscopic gastrostomy tube placement and fundoplication at 3 months of age. At almost 4 months of age, the infant acutely decompensated in the setting of abdominal compartment syndrome. She was unable to be resuscitated despite emergent exploratory laparotomy. The cause of this abdominal catastrophe was unknown, despite full autopsy.

Thrombocytosis was noted throughout the infant’s life, with a maximum recorded platelet count more than 3 times the upper limit of normal (1,247,000 per μl, Figure 1). There were no other consistently abnormal hematologic parameters on complete blood counts (Table 1). Thrombocytosis was unexpected, as platelet count derangement had not been previously described in clinical descriptions of *TRPV4*-related disease.

Though the etiology remained unclear despite subspecialist discussions, there was never an indication for intervention, treatment or other alteration in clinical management as a result of the high platelet count alone. The patient underwent one sepsis evaluation, which was triggered by acute respiratory decompensation where thrombocytosis was noted as evidence supporting the use of empiric antibiotics to rule out possible bacterial infection. When her blood culture remained negative after 48 hours, antibiotics were discontinued.

Discussion

TRPV4 mutations can cause autosomal dominant, life-limiting metatropic dysplasia. Clinical descriptions of the related skeletal manifestations are well documented,[1,2] as are potential associated clinical neuromuscular[5,6] and neuropathic[7,8] manifestations. To our knowledge, aberrancies in hematologic parameters have not previously been reported in association with human *TRPV4* mutation. However, *TRPV4* activation was recently linked to increased platelet production in mice.[3]

Clinically relevant *TRPV4* mutations have been described throughout the gene. Based on the recently solved TRPV4 protein structure, the mutation in this case falls in a region where other mutations have been associated with skeletal dysplasia.[9] We suspect that the E435K mutation represents a gain-of-function variant, based on autosomal dominant inheritance, its location, and related phenotypes. However, future molecular studies are needed to clarify the functional impact of this mutation.

Benign thrombocytosis may be a clinical component of *TRPV4*-associated metatropic dysplasia. Thrombocytosis observed in this case may have resulted from altered extracellular matrix stiffness and megakaryocyte reactivity, in agreement with cellular and murine phenotypes.[3] However, we cannot exclude chronic inflammation or respiratory support as potential confounders. Reactive thrombocytosis can occur in the setting of inflammation[10] or lung injury.[11] However, the magnitude and duration of this patient's thrombocytosis is outside the range of what we typically encounter in infants with lung disease. Notably, the platelet count was within the normal range for the first few days of this patient's life (Figure 1). This may represent relatively depressed platelet count values shortly after birth in this preterm infant, or alternatively reflect a postnatal reactive thrombocytosis. Indeed, one might expect a TRPV4 gain-of-function mutation to have made our patient more susceptible to reactive thrombocytosis. A small focus of extramedullary hematopoiesis was identified on autopsy of the lung in this patient, but we suspect that this was most likely an incidental finding of limited clinical consequence.

It is difficult to extrapolate generalized or mechanistic associations between *TRPV4* mutations and thrombocytosis from this case study alone. To validate the clinical association of platelet count and *TRPV4* mutation, it will be important to investigate hematologic phenotypes associated with other *TRPV4* mutations. Specific functional *TRPV4* perturbations may be reflected by altered platelet counts, similar to the spectrum of other *TRPV4*-associated clinical phenotypes.[1]

As an acute phase reactant, thrombocytosis can be a sign of infection, inflammation or other pathology.[10] In some clinical scenarios, particularly in critically ill neonates, thrombocytosis can lead to sepsis workups and/or other invasive procedures. As such, recognition of conditions that can cause thrombocytosis is important. In the reported case, thrombocytosis did not cause known clinical complications and was not associated with acute pathology. We hope that presenting this case may ultimately inform diagnostic workup in similar cases. However, until a link between *TRPV4* mutation and thrombocytosis can be confirmed in

other cases or case series, our report should not preclude or deter a detailed workup related to clinically observed thrombocytosis.

There was prognostic uncertainty in this case of *TRPV4*-associated metatropic dysplasia, although the prognosis was guarded based on respiratory support needs early in life. It might also be difficult to predict disease severity for some individuals with *TRPV4* variants of unknown significance. Platelet count might act as a non-invasive biomarker for TRPV4 function and/or disease severity in the right clinical context. This adds further importance for future studies to determine whether thrombocytosis correlates with *TRPV4* function and/or *TRPV4*-associated disease severity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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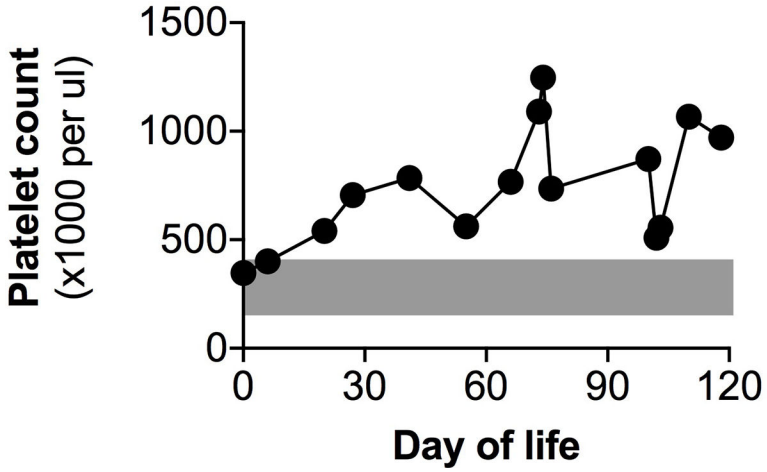

Figure 1.

Recorded platelet counts in this patient. Gray zone indicates normal reference range (150–400 ×1000 platelets per μl).

Table 1.

Hematologic trait values for this patient with associated normal reference ranges. Shown are the full range of laboratory values obtained, as well as the mean ± standard deviation for each parameter (n = 15 complete blood counts). PLT, platelet count. MPV, mean platelet volume. RBC, red blood cell count. Hb, hemoglobin. Hct, hematocrit. MCV, mean corpuscular volume. MCH, mean corpuscular hemoglobin. MCHC, mean corpuscular hemoglobin concentration. RDW, red cell distribution width. WBC, white blood cell count.

Trait	Normal Range	Range	Mean ± SD
PLT	150 – 400 ×1000/ul	347 – 1247	743 ± 266
MPV	9.0 – 10.9 fL	8.4 – 11.1	9.3 ± 0.9
RBC	3.1 – 4.5 ×10^6/ul	3.3 – 5.2	4.1 ± 0.6
Hb	9.5 – 13.5 g/dL	10.2 – 14.8	12.1 ± 1.8
Hct	29 – 41 %	30.3 – 44.8	35.9 ± 5.1
MCV	74 – 108 fL	81.5 – 100.5	87.8 ± 5.2
MCH	25 – 35 pg	26.6 – 36.0	29.7 ± 2.7
MCHC	30. – 36 g/dL	31.1 – 36.5	33.8 ± 1.3
RDW	35.2 – 45.1 fL	35.9 – 61.0	44.1 ± 8.1
WBC	6.0 – 13.3 ×1000/ul	7.7 – 29.6	14.7 ± 5.3