Scurvy Findings in a Child with Jacobsen Syndrome

A Case Report

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Abstract

Case: We describe the first reported case of scurvy developing secondary to behavioral traits of Jacobsen syndrome. The diagnosis of scurvy was significantly delayed because bleeding symptoms were initially attributed to baseline thrombocytopenia and platelet dysfunction associated with Jacobsen syndrome and patient's medication. Following vitamin C supplementation, signs and symptoms of the patient's disease quickly resolved.

Conclusions: We aim to reinforce the need to consider nutritional deficiencies in patients with complex medical histories and behavioral issues, especially when presenting with new complaints.

Vitamin C deficiency resulting in scurvy is a disease described ubiquitously throughout history and literature[1]. Although preventive measures have been known for centuries, scurvy continues to be present even in developed countries[2]. Most recent cases involve dietary shortcomings related to socioeconomic factors or behavioral barriers to adequate nutritional intake. Pediatric cases of scurvy are frequently related to food aversion and/or selectivity and lack vitamin supplementation or infants fed only evaporated or boiled milk[3].

Although multiple case reports have been published in the pediatric literature related to autism or cerebral palsy, we present here the first report of a patient with Jacobsen syndrome and a new diagnosis of scurvy[3-6]. Jacobsen syndrome represents a chromosomal deletion of 11q23[7-9] with common clinical manifestations including growth retardation, mental disability, craniofacial abnormalities, and thrombocytopenia or pancytopenia[7,9-11].

The patient was informed that data concerning the case would be submitted for publication, and her guardian provided consent.

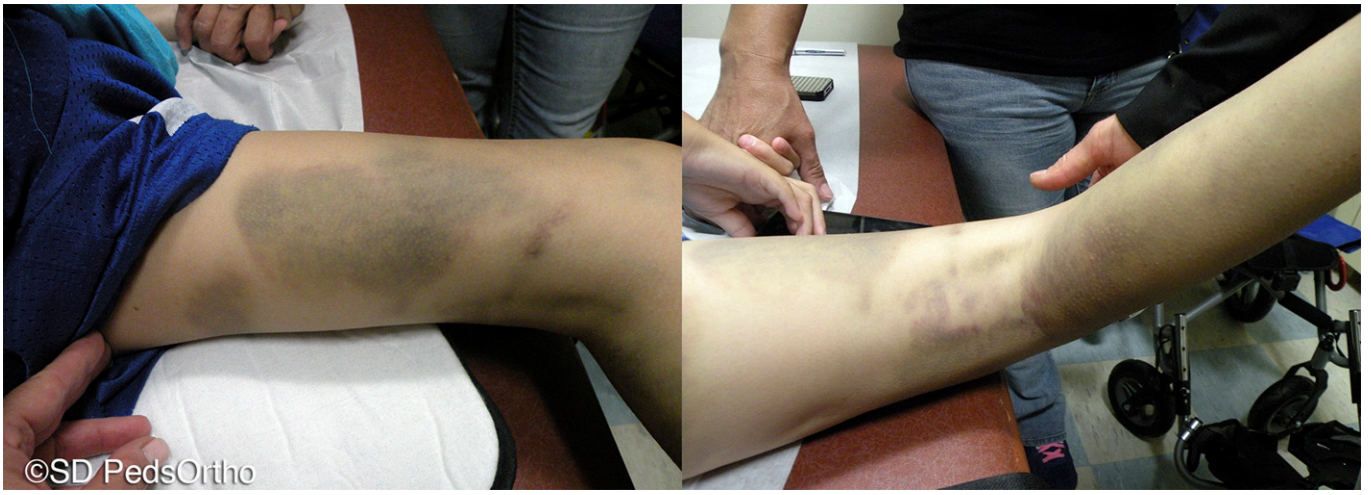

Fig. 1

Patient's presenting ecchymosis to her inner left thigh (left) and right popliteal fossa (right).

Disclosure: The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJSCC/A845).

TABLE I Patient's Presenting Lab Values on Admission Versus Normal Lab Values

Test	Patient Value	Normal Range
Vitamin C	<0.12 mg/dL*	0.20-1.90 mg/dL
Vitamin D 25-OH	18 ng/mL*	30-96 ng/mL
Copper	157 μg/dL	87-182 μg/dL
Zinc	55 μg/dL	25-148 μg/dL
Vitamin E α-tocopherol	4.8 mg/L	3.7-12.4 mg/L
Vitamin E β-tocopherol	2.0 mg/L	0.5-3.8 mg/L
Hemoglobin	9.2 GM/dL*	12.0-15.0 GM/dL
Hematocrit	28.5%*	35.0-45.0%
Platelet count	79,000/μL*	140,000-440,000/μL
Iron	43 μg/dL	30-120 μg/dL
TIBC	418 μg/dL*	250-400 μg/dL
Iron % saturation	10%*	15-50%
Ferritin	38 ng/mL	6-70 ng/mL
Reticulocytes	5.5%	0.5-1.5%
White blood cell	2,300/μL*	4,000-10,500/μL
C-reactive protein	0.6 mg/dL	0.00-0.99 mg/dL
Sedimentation rate	9 mm	0-20 mm

*Abnormal lab values.

Case Report

We present a 12-year-old girl with a medical history of Jacobsen syndrome with associated autism and attention-deficit hyperactivity disorder (ADHD) and recent onset of microcytic anemia not resolved with iron supplementation. The patient and family were informed and agreed to have data from this case published. Manifestations of Jacobsen syndrome for this patient included intellectual disability with limited verbal communication, growth retardation, musculoskeletal anomalies, and thrombocytopenia. She was known to the orthopaedic service because of tibial torsion, hallux valgus, and curly toes. In July 2012, she underwent an uncomplicated perioperative course for bilateral internal rotation tibia-fibula osteotomies and correction of her bilateral hallux valgus.

The patient presented to the hematology/oncology clinic in February 2013 with a history of weight loss and bleeding gums after brushing her teeth. She also reported bruising following needle sticks for lab draws, and bruising of her bilateral lower extremities. The patient's mother reported no known trauma or inciting events. A major factor that complicated this patient's presentation and the differential diagnosis was her known thrombocytopenia and platelet dysfunction attributed to Jacobsen syndrome. She also had recent increase in the dose of sertraline, which is known to interfere with platelet function. Her baseline platelet count ranged from 60,000 to 100,000/μL with an abnormal platelet function assay (PFA-100).

On physical examination, the patient had multifocal ecchymosis at various stages of evolution to her lower extremities (Fig. 1). She complained of lower extremity discomfort, but maintained the ability to ambulate. Her baseline knee flexion contractures of 10° appeared unchanged from previous visits. Laboratory findings were consistent with iron deficiency anemia (Table I). Given the patient's history of thrombocytopenia with platelet dysfunction and recent change in medication, the differential diagnosis supported abnormal bleeding related to platelet dysfunction[10].

Over the next weeks, the patient was evaluated by multiple clinical services due to worsening extremity bruising and gingival bleeding and eventual epistaxis. The nonaccidental trauma specialty service did not find any abuse-related concerns. At 3 months after symptom onset, the patient was admitted for unilateral lower extremity edema, knee effusion, and refusal to bear

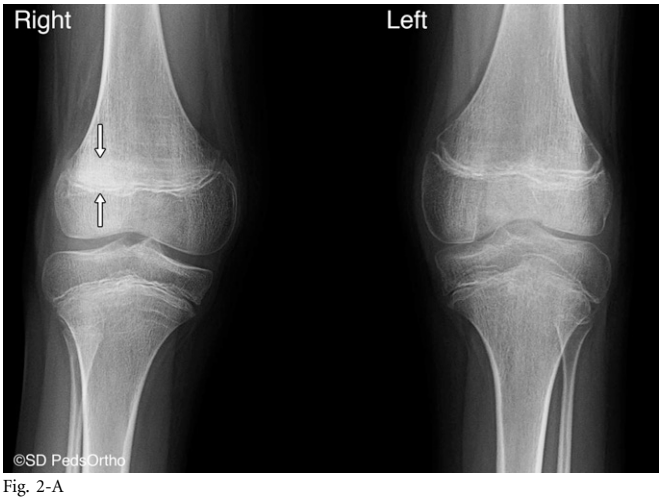

Fig. 2-A

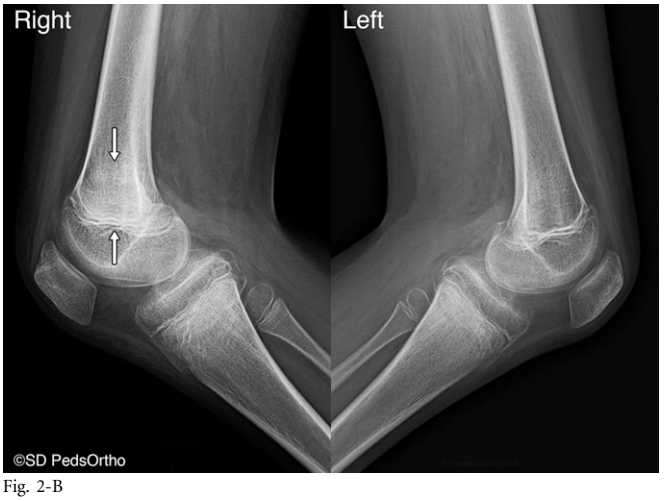

Fig. 2-B

Bilateral anterior-posterior (AP) (**Fig. 2-A**) and sagittal (**Fig. 2-B**) radiographs of the patient's knees demonstrating the subtle metaphyseal sclerosis consistent with a dense zone of provisional calcification.

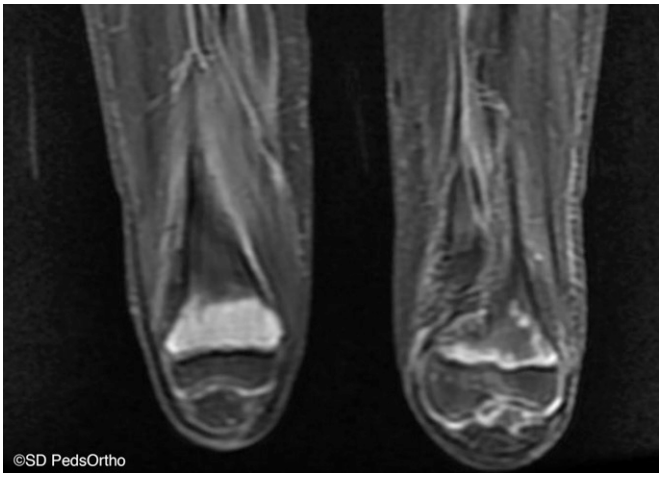

Fig. 3-A

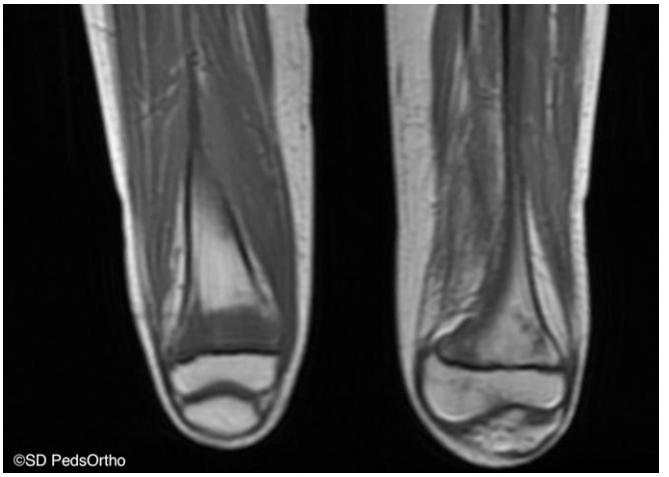

Fig. 3-B

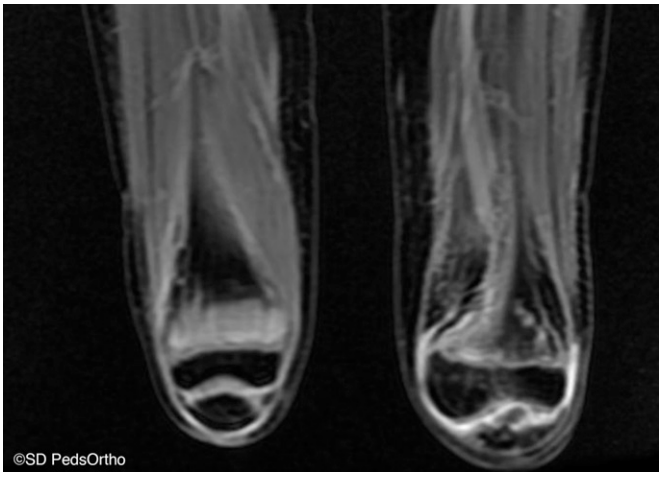

Fig. 3-C

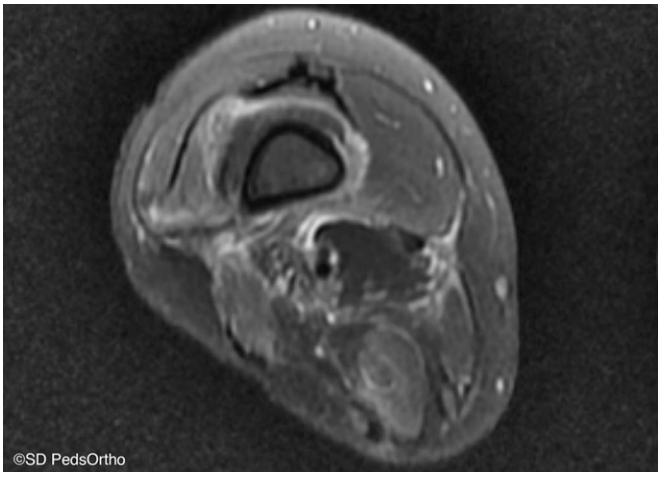

Fig. 3-D

MRI demonstrating findings of scurvy: (**Figs. 3-A through 3-C**) bilateral coronal images demonstrating the metaphyseal T1 hypointensity and T2 hyperintensity at the distal femoral metaphyses with patchy, near-symmetric areas of contrast enhancement. Periosteal elevation without definite subperiosteal collections suggested periosseous edema. There were multifocal areas of ill-defined T2 hyperintensity involving the soft tissues and muscles suggesting edema or hemorrhage, but no focal hematoma. There is also a left knee effusion. These are seen to enhance on **Fig. 3-C. Fig. 3-D** Midthigh STIR image demonstrating the abnormal diffuse T2 hyperintense signal involving the muscles and intermuscular fascial planes and soft tissue.

weight. Plain films demonstrated subtle metaphyseal sclerosis consistent with a dense zone of provisional calcification (Fig. 2). Magnetic resonance imaging (MRI) demonstrated bilateral femoral and tibial metaphyseal changes, as illustrated in Fig. 3.

There are rare reports in the literature about the MRI features of scurvy[4]. These have been ascribed to gelatinous transformation of the bone marrow. The multifocal involvement of bone marrow by near-symmetric signal changes on MRI, albeit nonspecific, made the radiologist suspicious of a systemic condition. Further history elucidated that the patient's diet consisted only of cheese burritos without fruit or vegetables. Laboratory tests confirmed the diagnosis of scurvy, given a vitamin C level of <0.12 mg/dL. Vitamin C supplementation and ongoing iron supplementation resulted in improvement of microcytic anemia, resolution of gum disease, and a return to weight bearing by her 2-week follow-up with orthopaedics. Her platelet count did normalize after vitamin C supplementation. Five years later, the patient still struggles with a balanced diet. She developed heavy menstrual bleeding and required supplementation for vitamin C and D deficiency and iron deficiency anemia.

Discussion

The similar clinical manifestations of scurvy and Jacobson syndrome rendered this patient's diagnosis challenging. Jacobsen syndrome, first described in 1973, is a rare disorder due to chromosomal deletion with[7,9-11] clinical manifestations that affect multiple systems[10,11]. Patients with Jacobsen syndrome have been found to have a high penetrance (88.5%) for Paris-Trousseau syndrome. Paris-Trousseau syndrome is characterized as transient neonatal thrombocytopenia plus persistent platelet dysfunction[7,9,11]. Thus, the coagulopathy that this patient had was initially attributed to the platelet dysfunction associated with Jacobsen syndrome.

The pathophysiology and treatment of scurvy has been thoroughly described dating back to 1550 BC[10,12]. Historians estimate that >2 million sailors died of scurvy during the Age of Sail culminating in "more deaths at sea than storms, shipwrecks, combat and all other diseases combined"[12]. The leading contributors to understanding scurvy were Dr. James Lind who wrote *Treatise on the Scurvy* in 1763 and Lieutenant James Cook who successfully sailed without scurvy throughout the 1700s by giving his sailors vitamin C–rich sauerkraut. He successfully circumnavigated the world without a single sailor contracting scurvy. These men influenced Sir Gilbert Blane to order lemon juice rations to the Royal Navy eliminating scurvy from the British Navy and aiding their defeat of Napoleon[12]. Ascorbic acid was finally discovered by the Hungarian biochemist, Albert Szent-Györgyi, winning him the 1937 Nobel Prize in Medicine[13].

Scurvy results from prolonged inadequate intake of the essential vitamin C or ascorbic acid. Vitamin C plays a role in many important biochemical pathways such as neurotransmitter synthesis, metabolism of cyclic nucleotides and prostaglandins, free radical antioxidants, and gut absorption of iron. The patient's anemia did not improve because of the patient's vitamin C deficiency and secondary lack of iron absorption. Scurvy's hallmark manifestation of poor collagen production results from vitamin C's role as a cofactor in hydroxylation of proline and lysine in collagen formation[8,10,13-15].

Clinical manifestations of scurvy have a wide range of presentations that initially present within 8 to 12 weeks of low vitamin C intake, but the full spectrum of symptoms can take months of deficiency to develop. However, 24 hours following vitamin C supplementation to reverse the deficiency, signs can improve, but a full recovery can take months. Many of the clinical findings of scurvy are related to its role in collagen, such as hyperkeratosis, cork screw hair, ecchymosis, gingival bleeding, and eventual epitaxis, as observed in our patient. Some reports indicate a lack of vitamin C can reduce platelet aggregation and result in platelet dysfunction as well[8,15,16]. Subperiosteal hemorrhages can occur, leading to edema, contractures, and severe bone and joint pain[8,10].

Radiographic findings in scurvy are well described in the literature. Radiographs may be normal in mild disease, but advanced disease can present as fractures. Aside from diffuse demineralization and growth arrest/recovery lines, radiographs can demonstrate periosteal elevation and shell-like calcifications from subperiosteal hemorrhage, sclerotic epiphyseal rims (ring sign of Wimberger), dense zones of provisional calcification in the metaphysis (Frankel sign), and metaphyseal spurs (Pelkan spur) or cupping with physeal widening. Other characteristic findings include cortical thinning and trabecular indistinctness[4,17,18]. The findings in our patient were limited to subtle metaphyseal sclerosis consistent with a dense zone of provisional calcification.

MRI findings in scurvy are difficult to interpret without radiographs and clinical information due to the nonspecific appearances also seen in osteomyelitis, marrow regeneration, marrow replacement, or nonspecific marrow edema. As in our patient, findings included marrow signal changes with areas of T1 hypointensity and T2 hyperintensity in the metaphyses or metadiaphyses (Fig. 3). These characteristics are thought to be from intraosseous edema or likely hemorrhage[3-6]. Marrow changes of scurvy sometimes enhance with contrast. The subperiosteal hemorrhages and periosseous edema in our patient represent more characteristic findings[6].

Despite vast knowledge and awareness of vitamin C deficiency's sequelae, it is still reported in modern day. A 2003 to 2004 national survey reported that the overall age-adjusted prevalence was 7.1% in Americans, which is down from 13% in the last survey from 1988 to 1994[8,19]. Reports indicate that high-risk populations are smokers, obese persons, and patients with medical, social, and/or psychiatric barriers to a balanced diet[8]. Clinicians must also remain vigilant in considering a broad differential diagnosis in challenging, complex cases.

In modern day, the diagnosis of scurvy is often delayed. The pediatric patients diagnosed with scurvy today have significant medical, social, and/or psychiatric conditions that result in poor nutrition. Our patient with Jacobsen syndrome highlights the concern for behavioral influences of food aversion for proper nutritional intake. It is unclear whether the food aversion is directly related to Jacobsen syndrome; however, it is not uncommon for infants and young children to have abnormalities of the gastrointestinal tract resulting in feeding difficulties. In addition, this child had autism and ADHD, and their association with food aversion and selectivity were likely the primary contributor to this child's feeding behavior[20]. We aim to reinforce the need to consider nutritional deficiencies in these pediatric orthopaedic patients, especially when presenting with new complaints of edema, bruising, and imaging changes even in patients with medical histories that explain clinical symptoms. As demonstrated with the recurrence in our patient, physicians must stay vigilant and follow these patients in the long term. ■

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