An Orange a Day Keeps the Doctor Away: Scurvy in the Year 2000

Michael Weinstein, MD*; Paul Babyn, MD‡; and Stan Zlotkin, MD*

ABSTRACT. Scurvy has been known since ancient times, but the discovery of the link between the dietary deficiency of ascorbic acid and scurvy has dramatically reduced its incidence over the past half-century. Sporadic reports of scurvy still occur, primarily in elderly, isolated individuals with alcoholism. The incidence of scurvy in the pediatric population is very uncommon, and it is usually seen in children with severely restricted diets attributable to psychiatric or developmental problems. The condition is characterized by perifollicular petechiae and bruising, gingival inflammation and bleeding, and, in children, bone disease. We describe a case of scurvy in a 9-year-old developmentally delayed girl who had a diet markedly deficient in vitamin C resulting from extremely limited food preferences. She presented with debilitating bone pain, inflammatory gingival disease, perifollicular hyperkeratosis, and purpura. Severe hypertension without another apparent secondary cause was also present, which has been previously undescribed. The signs of scurvy and hypertension resolved after treatment with vitamin C. The diagnosis of scurvy is made on clinical and radiographic grounds, and may be supported by finding reduced levels of vitamin C in serum or buffy-coat leukocytes. The response to vitamin C is dramatic. Clinicians should be aware of this potentially fatal but easily curable condition that is still occasionally encountered among children. Pediatrics 2001; 108(3). URL: http://www.pediatrics.org/cgi/content/full/108/3/e55; scurvy, hypertension, magnetic resonance imaging, bone pain.

ABBREVIATION. MRI, magnetic resonance imaging.

A 9-year-old girl with global developmental delay presented with signs of scurvy secondary to long-term ascorbic acid deficiency and was also discovered to have severe hypertension. This case highlights a rare disease that still exists in the pediatric population and points to a possible association between hypertension and vitamin C deficiency. Magnetic resonance imaging (MRI) findings of scurvy, which have been previously unreported, are described.

CASE REPORT

A 9-year-old girl was admitted to hospital because of musculoskeletal pain, inflammatory gingival disease, and hypertension. Her past medical history was remarkable for moderate global developmental delay, mild facial dysmorphism, and a seizure disorder managed with long-term phenytoin administration. She had 2 older sisters with a similar disorder, and a previous evaluation had not identified a known, inherited condition.

She was admitted to a community hospital with a 2-month history of increasing bilateral knee pain and swollen, bleeding gums. There was no history of fever, weight loss, trauma, obviously swollen joints, petechiae, or bruising. At the time of her hospitalization, the child refused to walk. She previously ambulated with the aid of a walker.

Investigations at that time revealed a hemoglobin of 79 g/L, white blood cell count of 8.9 × 10^9/L with a normal differential count and a platelet count of 470 × 10^9/L. A blood smear showed hypochromic, microcytic red blood cells; no malignant cells were seen. The erythrocyte sedimentation rate was elevated at 62 mm/hour. The C-reactive protein level was 125 mg/L (reference range: 0–8 mg/L). Radiographs of the knee showed osteopenia, and a bone scan initially showed increased uptake around the left knee. She was treated presumptively for osteomyelitis with intravenous clindamycin, but after 2 weeks of therapy, there was no improvement, and a repeat bone scan was interpreted as normal. Additional studies included a negative antinuclear and rheumatoid factor, and normal complement, creatine kinase, calcium, phosphate, alkaline phosphatase, and parathyroid hormone levels. She required regular ibuprofen and codeine for analgesia. Because of her gingival disease, which was felt to possibly be secondary to phenytoin, she underwent a gingivoplasty and dental extractions.

The biopsy showed chronic inflammatory cells in the submucosa without evidence of malignancy. Although in hospital, hypertension was noted with blood pressure measurements ranging from 130 to 170/80 to 110 mm Hg. She was transferred to a tertiary care institution for additional evaluation.

On physical examination, weight and height were between the 10th and 25th percentiles for age. Her blood pressure was 160/110 mm Hg. She had mild, dysmorphic features with epicanthic folds, mid-face hypoplasia, broad nasal tip and short, broadened hands. She had markedly swollen, purple, spongy gingiva which bled spontaneously (Fig 1). Her cardiovascular examination was normal with no blood pressure gradient between her upper and lower extremities. There was no hepatosplenomegaly or lymphadenopathy. Musculoskeletal examination showed soft-tissue swelling of the distal wrists and left suprapatellar area. She had decreased range of motion of her knees bilaterally with a fixed flexion contracture of 30° at the left knee. There were no joint effusions. Her skin showed follicular hyperkeratosis with perifollicular purpura of the lower extremities. Neurologic examination was normal.

A skeletal survey revealed generalized osteopenia, evidence of T7-T10 vertebral compression fractures, and dense lines at the distal left femoral metaphysis. The findings were not felt to be indicative of rickets, scurvy, or a storage disorder. A bone scan showed increased uptake only at sites corresponding to the vertebral compression fractures. An MRI study showed a diffuse, symmetrically abnormal signal involving the distal femoral metaphyses and epiphyses, both iliac bones, distal radii, and soft tissue surrounding the knees (Fig 2).

Initial concern was whether a malignant process was responsible for her presentation. A bone marrow aspirate and biopsy showed no evidence of malignancy or storage cells. There were no stainable iron stores. Biopsy of the distal femoral metaphysis showed nonspecific fibrous changes with no evidence of malignancy. The constellation of bone and gingival disease, follicular hyperkeratosis, and perifollicular purpura strongly suggested a diagnosis of scurvy. The patient’s diet consisted of water, com-
commercial chocolate puddings and cakes, occasional jarred semipureed foods (beef, spaghetti), and 2% milk (8 oz/d). She took no vitamin supplements. By her family’s recollection, she had not consumed fresh fruits or vegetables or fruit juices for 5 to 6 years because of her limited preferences. Review of the nutritional content of her diet revealed essentially no dietary source of vitamin C for at least several years and limited amounts of vitamin D and iron (Table 1). Serum ascorbic acid level was 27 μmol/L (normal: 11–85 μmol/L), but the sample was taken after several weeks of consumption of hospital meals and is therefore not reflective of total body stores. Nutritional laboratory study results showed low levels of serum ferritin (16 μg/L; normal: 22–400 μg/L), iron (0.6 μmol/L; normal: 9–27 μmol/L), 25-OH-vitamin D (16 nmol/L; normal: 25–90 nmol/L), and 1, 25-OH-vitamin D (32 pmol/L; normal: 40–140 pmol/L). Serum B12 and red blood cell folate levels were normal.

Investigations done for her hypertension included normal urinalyses, blood urea nitrogen, creatinine, Doppler renal ultrasound, diethylenetriaminepentaacetic acid renal scan, serum renin, and 24-hour urine vanillylmandelic acid and homovanillic acid levels. Her electrocardiogram and echocardiogram showed borderline left ventricular hypertrophy.

The child and family were assessed by the clinical genetics and metabolics services. The skeletal survey was not felt to be suggestive of a lysosomal storage disease. Investigations including a karyotype on peripheral blood, urine for oligosaccharides, mucopolysaccharides, and organic acids, leukocyte assays for β-galactosidase and hexosaminidase, and blood for quantitative amino acids, lactate, and ammonium were normal. A skin biopsy was performed for additional fibroblast cultures. No diagnosis of the underlying condition affecting the child and her siblings was established, and the family continues to be followed by the genetics service.

Treatment was started with 250 mg of vitamin C, 800 U of vitamin D, iron and calcium supplementation, and 1 multivitamin daily. Her family was educated about dietary modification, and her blood pressure was controlled on amlodipine and nadolol. Within 1 week of starting vitamin supplementation, her gingival bleeding and perifollicular purpura resolved, gingival swelling was markedly improved (Fig 3), and she no longer required analgesia. There was significant improvement in the soft-tissue swelling of the radii and knees and almost full range of motion of her knees. Weight-bearing exercises were gradually introduced because of her osteopenia and compression fractures. Ten days after starting vitamin C supplementation, repeat radiographs of the lower extremities (Fig 4) showed fractures in the area of the left medial femoral metaphysis and a line of increased density surrounding the epiphysis (Wimberger ring). Her hemoglobin increased to 125 g/L and her C-reactive protein normalized (6.6 mg/L; normal: 0–8 mg/L) after 2 weeks of treatment. She was
ambulating with a walker as she had done previously by 6 weeks and at her most recent follow-up after 6 months, her blood pressure was within normal limits for age while off all hypertensive medications. A radiograph of the left knee demonstrated resolution of the metaphyseal spurs and lucencies, consistent with interval healing (Fig 5).

DISCUSSION

Unlike most animals, human beings lack the ability to convert glucose to ascorbic acid (vitamin C) via gulonolactone oxidase, so that ascorbic acid in the form of fresh fruits, vegetables, or vitamin supplements is an essential nutrient in the human diet.1

Fig 3. Photograph demonstrating significant improvement in gingival swelling and resolution of gingival bleeding 10 days after treatment with vitamin C.

Fig 4. Anteroposterior radiograph of the left knee showing demineralization, metaphyseal lucent bands, and irregularity of the medial cortex of the distal femoral metaphysis in keeping with fractures (arrow).

Fig 5. Anteroposterior radiograph of the left knee performed after 6 months of vitamin C, showing healing in the region of the distal femoral metaphysis (arrow).
Scurvy has been known to exist for more than 3 millennia with a description of a condition similar to it recorded by the ancient Egyptians in the Ebers papyrus.\textsuperscript{2} Not until 1753, however, was scurvy and its prevention by citrus fruits systematically described by Sir James Lind, and ascorbic acid was first isolated in 1928.\textsuperscript{3} By the middle of the 20th century, technological developments including food processing and transportation combined to make scurvy a rarely encountered disease. In a historical review by Lee\textsuperscript{4} of the medical records of the Yale-New Haven Hospital from 1941 to 1971, there were 10 children with a diagnosis of scurvy, all occurring before 1949. Scurvy is still occasionally encountered, predominantly among elderly, indigent persons who live alone and prepare their own food, as well as in alcoholics and food faddists. Scurvy is less common in the pediatric population, but case reports still appear.\textsuperscript{5,6} Groups at risk include infants who are fed evaporated or boiled milk, in which ascorbic acid is destroyed by heat and children with dietary restrictions stemming from psychiatric or developmental disorders, such as the child described here.

Ascorbic acid is a necessary cofactor in collagen biosynthesis, and it is felt that the capillary fragility responsible for the clinical manifestations of scurvy is attributable to the depletion of pericapillary collagen.\textsuperscript{7} Ascorbic acid has numerous physiologic properties, however, and other mechanisms are likely involved. Signs of scurvy develop after 1 to 3 months of inadequate vitamin C intake, depending on existing body stores.\textsuperscript{8} The earliest manifestations are dermatologic, with petechiae, ecchymoses, hyperkeratosis, and corkscrew hairs appearing at the onset of naturally and experimentally-induced scurvy.\textsuperscript{9} As in our patient, the purpura is often localized to the perifollicular area. Gingival disease, characterized by swelling, ecchymoses, bleeding, and loosening of the teeth, usually occurs next in dentulous patients, also secondary to blood vessel instability. In contrast to adults, bone disease is a frequent manifestation of the condition in children, and, as in our patient, can be debilitating. Pathologically, there is a defect of osteoid matrix formation and cartilage resorption leading to disordered bone structure and subsequent fractures around the growth plates.\textsuperscript{10} In addition, subperiosteal hemorrhages can occur, leading to bone pain. Anemia is another hallmark of scurvy and is multifactorial in nature. Iron deficiency anemia is common and may be secondary to a combination of bleeding, other dietary deficiencies, and decreased absorption. Ascorbic acid improves iron absorption by reducing it to the more absorbable ferrous state,\textsuperscript{11} and in our patient, who had absent bone marrow iron stores, the anemia only improved after vitamin C administration, despite 6 weeks of previous iron supplementation. Although nonspecific, an elevated erythrocyte sedimentation rate and C-reactive protein may be seen,\textsuperscript{5,10} which most likely reflects the inflammation involved in the bone and gingiva as was seen on biopsy in our patient. Other clinical signs of scurvy include skeletal muscle degeneration, cardiac hypertrophy, diminished adrenal and bone marrow function, psychological changes, arthritis, poor wound healing, edema, and alopecia.\textsuperscript{12} The role of other concurrent nutritional deficiencies and medical conditions, however, contribute to clinical heterogeneity. Untreated scurvy can be fatal, with death ensuing from fulminant bacterial or tuberculous infection possibly related to poor wound healing,\textsuperscript{13} cerebral hemorrhage, or hemopericardium.\textsuperscript{14}

One aspect of this case that needs to be addressed is whether this child’s presentation can be attributed simply to a combination of rickets and iron deficiency. In fact, childhood scurvy was thought to be a complication of rickets until it was described as a separate entity in 1883.\textsuperscript{15} In contrast to experimentally-induced scurvy, people with naturally acquired disease often have generally deficient diets, which can contribute to the clinical presentation. However, this child’s gingival disease and skin manifestations cannot be explained by other nutritional deficiencies. Although a component of this child’s bone disease may have been exacerbated by vitamin D deficiency, the radiographic findings were not suggestive of rickets, and the normal levels of calcium, phosphate, alkaline phosphatase, and parathyroid hormone do not support vitamin D deficiency rickets as the primary cause of the child’s bone disease.

An unusual aspect of this case was the presence of severe hypertension without an apparent secondary cause, despite a thorough investigation. Postural hypotension and syncope are reported to be common in untreated scurvy. Conversely, a preterminal event in this condition may be frank hypertension progressing to shock. Ascorbic acid is involved physiologically in catecholamine biosynthesis and secretion,\textsuperscript{16} and there are animal and human data, which suggest a relationship between vitamin C status and blood pressure.\textsuperscript{17,18} It has been found that vitamin C levels in spontaneously hypertensive rats are lower than in controls, and that vitamin C supplementation decreased blood pressure in this rat model.\textsuperscript{19} Furthermore, epidemiologic studies have found a negative correlation between vitamin C levels and blood pressure, and several small-scale intervention trials have reported a decrease in blood pressure in borderline hypertensives using vitamin C supplementation.\textsuperscript{20} The resolution of this child’s hypertension along with her other signs of scurvy after treatment with vitamin C is suggestive of a causal relationship between her hypertension and clear vitamin C deficiency.

As in the case illustrated here, other conditions such as leukemia, musculoskeletal infections, and vasculitides are often considered before the diagnosis of scurvy is made because of the rarity of the condition. A review of the medical records from 1980 to the present at our institution, which is a tertiary care pediatric facility with >50 000 emergency department visits per year, revealed 1 additional diagnosis of scurvy. This patient was a teenaged female with an eating disorder who had gingival bleeding and perifollicular purpura. The most important factor in making the correct diagnosis is maintaining a high index of suspicion in the right clinical scenario. The “four H’s” are a useful device for remembering many of the common presentations of scurvy: hem-
or hemorrhagic signs, hyperkeratosis, hematologic abnormalities, and hypochondriasis.1 In addition to clinical signs, radiologic studies can be helpful. The most common radiographic finding, however, is osteopenia, which is nonspecific, and the more specific signs for scurvy are less common and likely to be unfamiliar to many radiologists because of the rarity of the condition. Other radiographic findings include the preservation of the zones of calcification at the distal metaphyses with an adjacent lucency, referred to as the scurvy zone through which fractures may occur, Pelkan spurs, which are the result of healing fractures at the periphery of the zone of calcification, and an increased density outlining the epiphyses (Wimberger ring).21 Periosteal bone may be seen along the shafts of the long bones when subperiosteal bleeding occurs. Often, as in the present case, the radiographic findings are more pronounced once treatment is initiated and new bone is able to form.

MRI findings in scurvy will reflect the underlying pathophysiology, with areas of hemorrhage seen within bones at sites of fracture and in the periosteum with low signal or intermediate signal on T1-weighted imaging and high signal on T2-weighted images. MRI may be performed because of the frequent suspicion of malignancy, especially leukemia. MRI in scurvy will not show the diffuse marrow changes typically seen in leukemia.

A low level of plasma vitamin C is specific in this condition, but it may be normal if there has been recent ascorbic acid intake (as was the case in our child) making it an insensitive diagnostic test for vitamin C deficiency.5,6,22 Measuring vitamin C levels in buffy-coat leukocytes better reflects body stores,23 but this is technically more difficult and was not readily available in our case. Another indicator of body stores22 is the measure of urinary excretion of an intravenous dose of vitamin C, 80% should be excreted within 5 hours in the setting of adequate body stores.12

Finally, the best evidence of the presence of scurvy is the resolution of the manifestations of the disease after ascorbic acid treatment. The dose and duration of treatment should be individualized. It has been demonstrated that as little as 10 mg of vitamin C per day can cure scurvy in human volunteers.1 Infants and children are usually treated with 100 to 300 mg daily and adults 500 to 1000 mg daily for 1 month or until full recovery occurs.16,24–26 Spontaneous bleeding as well as oral and constitutional symptoms generally significantly improve within days while bone abnormalities and ecchymoses gradually improve over several weeks.1,16,24–26 The duration of symptoms and the presence of other nutritional deficiencies influence the rate of recovery. In our child, vitamin D deficiency from deficient intake or associated with long-term phenytoin use may have played a role in her bone disease.

Although rare, scurvy remains a condition that is still encountered in the pediatric population, especially among certain groups with unusual eating habits. A heightened awareness is needed to avoid unnecessary tests and procedures and to be able to implement treatment for a potentially fatal but easily curable disease.

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