Review

Musculoskeletal manifestations of scurvy

Olivier Fain

Internal Medicine Department, Jean Verdier Teaching Hospital, Assistance Publique-Hôpitaux de Paris, Paris-North University-School of Medicine, UPRES EA 3409, avenue de 14 Juillet, Bondy cedex 93143, France

Received 20 October 2003; accepted 8 January 2004

Available online 09 April 2004

Abstract

Scurvy occurs in individuals who eat inadequate amounts of fresh fruit or vegetables, often because of dietary imbalances related to advanced age or homelessness. Asthenia, vascular purpura, bleeding, and gum abnormalities are the main symptoms. In 80% of cases, the manifestations of scurvy include musculoskeletal symptoms consisting of arthralgia, myalgia, hemarthrosis, and muscular hematomas. Vitamin C depletion is responsible for structural collagen alterations, defective osteoid matrix formation, and increased bone resorption. Imaging studies may show osteolysis, joint space loss, osteonecrosis, osteopenia, and/or periosteal proliferation. Trabecular and cortical osteoporosis is common. Children experience severe lower limb pain related to subperiosteal bleeding. Laboratory tests show nonspecific abnormalities including anemia and low levels of cholesterol and albumin. The finding of a serum ascorbic acid level lower than 2.5 mg/l confirms the diagnosis. Vitamin C supplementation ensures prompt resolution of the symptoms.

© 2004 Elsevier SAS. All rights reserved.

Keywords: Scurvy; Vitamin C; Vitamin deficiency; Hemarthrosis; Osteoporosis; Barlow’s disease

1. Introduction

Scurvy, the constellation of clinical manifestations caused by vitamin C deficiency, has been increasingly reported over the last few years [1–12]. Individuals with risk factors for poor nutrition, such as social isolation, poverty, and homelessness, provide most cases of scurvy, although no subset of the general population is exempt. Musculoskeletal manifestations may be the presenting symptoms.

2. Historical perspective

Scurvy was known in Ancient Egypt, and a description ascribed to Hippocrates explains that “sufferers have a foul breath, boggy gums, and a propensity for nosebleeds; they may have leg ulcers.” Between the 15th and 18th centuries, scurvy took the lives of 50–80% of those who embarked on long sea voyages. In 1753, James Lind, a British Naval Surgeon, reported that eating oranges and lemons was effective against scurvy. Lemon juice was provided preventively to sea voyagers in Britain starting in 1795 and in France starting in 1856 [13]. In 1907, Holst and Frolisch induced scurvy in guinea pigs by feeding them a diet low in fresh vegetables. Five years later, Zylva extracted an antiscorbutic compound from lemon juice. Finally in 1932, Haworth elucidated the structure of vitamin C and suggested the name “ascorbic acid”. Reichstein succeeded in synthesizing ascorbic acid a few months later.

3. Metabolism

Vitamin C, or ascorbic acid, is a water-soluble compound vulnerable to heat, ultraviolet radiation, and oxygen. The total pool in the body is 1500–2500 mg and the daily turnover is 45–60 mg, i.e. about 3% of the total [14]. Vitamin C has a half-life of 10–20 days. Absorption occurs in the ileum via an active transport mechanism that becomes saturated when the oral intake exceeds 180 mg/day. The absorption rate is about 85%. Concentrations are in the 5–15 mg/l range in the plasma and erythrocytes but are 80 times higher in the platelets and erythrocytes. Levels in tissues are similar to those in leukocytes. Vitamin C is not stored in the body, so that some dietary intake is indispensable, the best sources being fresh fruit and vegetables. Milk, fish, and meat contain little or no vitamin C (0–2 mg/100 g). To prevent scurvy, the daily intake must be no lower than 10 mg/day and the body pool no smaller than 350 mg [15].
Vitamin C is involved in numerous hydroxylation reactions, including those responsible for procollagen production via the enzymes proline-oxidase and lysine-oxidase. Vitamin C deficiency induces collagen abnormalities that explain the clinical manifestations of scurvy: abnormal dentine production and loss of teeth, vessel wall damage and bleeding, purpura, edema, bone changes (in children) due to the inability of osteoblasts to produce the osteoid seam, and skin changes related to keratin abnormalities. The effect of vitamin C on dioxygenases is essential to the production of carmine, and this may explain the fatigue experienced by patients with scurvy. Vitamin C is a cofactor in the biosynthesis of catecholamines, most notably in the conversion of dopamine to norepinephrine, which may explain the behavior and mood disorders associated with vitamin C deficiency. Vitamin C increases the absorption of nonheme iron [15].

4. Epidemiology

Vitamin C deficiency remains common. Studies done in the 1970s in the United Kingdom found serum ascorbic acid levels lower than 2 mg/l in 50% of elderly individuals living at home [16]. In 1998, Johnston reported vitamin C deficiency (<2 mg/l) in 6% and depletion (<5 mg/l) in 30.4% of apparently healthy middle-class Americans [17]. In a study from the Val-de-Marne region near Paris, France, in 1108 non-hospitalized individuals, Hercberg found that serum ascorbic acid levels were lower than 2 mg/l in 5% of women and 12% of men overall, and that these proportions increased to 15% and 20%, respectively, in the subset older than 65 years of age [18]. We prospectively investigated 184 patients admitted to an internal medicine department in Seine-Saint-Denis, also near Paris, France; serum ascorbic acid levels were lower than 5 and 2 mg/l in 47.3% and 16.9% of patients, respectively. In some geographic areas, scurvy remains a scourge: thus, over 100 000 cases were recorded in the 1990s among refugees in the horn of Africa [20]. Ascorbic acid levels vary across seasons, with levels being lowest during the winter [21].

5. Risk factors for vitamin C deficiency

An inadequate intake of fresh fruit and vegetables is by far the main cause of vitamin C deficiency. Males who live alone, older individuals, chronic alcoholics, and individuals who voluntarily eat a restrictive diet or eat only in fast-food restaurants are at high risk for low vitamin C intake. The two risk factors identified in our study [19] were being retired and abusing alcohol and cigarettes. Jacob et al. [22] reported that vitamin C deficiency was more common among males, whereas Johnston and Thompson [17] found no difference between males and females. Smoking decreases the intestinal absorption and increases the catabolism of vitamin C.

Thus, smoking more than 20 cigarettes per day is associated with a 40% increase in the daily vitamin C turnover, as compared to nonsmokers [23]. Schectman [24] reported that smokers had a threefold increase in vitamin C deficiency and estimated that they needed a daily intake greater than 200 mg/day. Kallner et al. [23] showed that alcohol increases vitamin C requirements.

A study was done in Paris, France, in 87 individuals who had been homeless for longer than 2 years. Among them, 84% were chronic alcoholics and 75.5% were smokers. Vitamin C assays showed depletion in 95% of cases and undetectable levels in 72% [25]. Other factors associated with vitamin C deficiency include psychosis and anorexia nervosa; cancer [26], AIDS, and other wasting diseases; parenteral nutrition without appropriate vitamin C supplementation; renal replacement therapy by hemodialysis or peritoneal dialysis, which is associated with increased vitamin C needs; gastrointestinal disorders responsible for decreased vitamin C absorption such as Crohn’s disease [27], Whipple’s disease [28], and celiac disease [29]; and increased needs related to growth, pregnancy, and breast-feeding. Insulin-dependent diabetes mellitus is also associated with increased needs: even with a dietary intake within the recommended range, patients with insulin-dependent diabetes have low vitamin C levels in leukocytes [30] and blood [17]. Finally, renal vitamin C wasting may occur in patients with iron overload disorders [31].

6. Clinical manifestations

Models of scurvy have provided accurate information on the time to development of clinical manifestations. Serum ascorbic acid levels become undetectable 41 days after the initiation of a diet deficient in vitamin C, cell depletion occurs after 121 days, and the first skin lesions develop after 132 days. Dental abnormalities occur after 6 months. The constellation of clinical symptoms develops after 1–3 months of a diet containing no vitamin C at all, when the total body pool falls below 300 mg and the serum ascorbic acid level decreases below 2.5 mg/l [17,19]. Hodges reported that the first clinical manifestations of scurvy occurred when serum ascorbic acid levels fell to the 1.3–2.4 mg/l range in five patients with experimental vitamin C deficiency [31]. The earliest manifestations are nonspecific constitutional symptoms such as asthenia, anorexia, and weight loss.

6.1. Musculoskeletal manifestations

These symptoms develop later and consist of arthralgia in the knees, ankles, and wrists, as well as myalgia [32]. Musculoskeletal manifestations are present in 80% of patients with scurvy [33]. Eventually, bleeding occurs within the joints, mainly the hips, knees, and ankles, the two main mechanisms being damage to synovial blood vessels and microfractures [33]. Involvement of the hip may produce radiographic osteolysis [34,35], sometimes with joint space
loss [35]. Other radiographic changes may include osteonecrosis, osteopenia, and cortical thinning with periosteal proliferation [36]. Computed tomography shows bone loss, cortical disruption, and joint effusion [34,35]. Increased uptake is seen on radionuclide bone scan images. These findings may suggest malignant osteolysis, septic arthritis, or osteonecrosis. Histologic examination of specimens taking during hip arthroplasty [34] have shown hemorrhagic bone infarctions with cartilage destruction. Electron microscopy examination of the synovial membrane of a patient with scurvy showed loss of mature collagen fibers in the interstitial and perivascular areas [37].

Osteoporosis affecting both the trabecular and the cortical bone seems common in patients with scurvy [38]. Vitamin C depletion results in defective osteoid matrix formation and in increased bone resorption. Radiographs show nonspecific changes such as biconcave vertebral deformity with sclerosis of the edges [39]. Osteoporotic vertebral fractures have been reported [40,41]. However, in the case described by Barratt and Summers [42] the causal role for vitamin C deficiency was questionable, as the patient was a 71-year-old woman who had experienced the menopause at 43 years of age. In older individuals, multiple deficiencies are the rule, and concomitant vitamin D deficiency increases the risk of vertebral fracture. Using the data from the Postmenopausal Estrogen/Progestin Interventions Trial [43], Hall showed that supplementation with 100 mg/day of vitamin C was not associated with an increase in bone mineral density (BMD) in women with a low dietary calcium intake (<500 mg/day) but resulted in a significant BMD increase at the femoral neck in women with adequate calcium intakes. Morton investigated the effects of vitamin C supplementation (mean dosage, 745 mg/day, for longer than 3 years) in postmenopausal women and found a significant BMD increase as compared to the controls [44]. In addition, vitamin C supplementation acted synergistically with estrogens and calcium [44].

Studies of potential links between vitamin C deficiency and osteoarthritis have produced conflicting results. McAlindon et al. [45] reported slowing of the rate of joint space loss and decreased pain in patients with knee osteoarthritis who took large supplements of vitamin C and other antioxidants (vitamin E and beta-carotene). Wluka, in contrast, found that antioxidants failed to improve cartilage volume or pain in patients with knee osteoarthritis [46].

Musculoskeletal manifestations are prominent in pediatric scurvy or Barlow’s disease [47]. In 1883, Thomas and Barlow described 31 cases of rickets, concluding that “acute rickets” was actually scurvy, sometimes accompanied with genuine rickets [48]. Autopsy findings led him to ascribe the severe lower limb pain to bleeding in the subperiosteal space. Scurvy affect infants aged 6–18 months who are fed only formula without vitamin C supplementation. Breast milk contains enough vitamin C to meet the infant’s needs, provided the mother does not have vitamin C deficiency. The constitutional symptoms of scurvy in infants include failure to gain weight, loss of appetite, and irritability. Severe pain in the thighs and legs is a striking feature of infantile scurvy and can result in pseudoparalysis. Subperiosteal hematomas may be palpable as painful swellings over the distal ends of the femurs and tibias. Radiographs show sheathing of the physeal shafts, broadening of the calcification front at the anterior end of the ribs and ends of the metaphyses, and demineralization with metaphyseal fractures.

6.2. Other clinical manifestations

Bleeding, which is a consequence of vessel wall fragility, manifests primarily as petechiae over the limbs and trunk centered on the hair follicles, bruising, and hematomas. Bleeding within nerve sheaths is responsible for “painful scurvy paralysis”. Intramuscular hematomas may cause compartment syndrome. Gastrointestinal, gynecological, and cerebral bleeding has been described. Follicular hyperkeratosis and pigmented ichthyosis may occur, together with lower limb edema, oarscrew body hair, and alopecia.

Oral cavity abnormalities are characteristic although inconsistent. Hypertrophy and bleeding of the gums occur only in patients with teeth, being more marked in patients with a poor dental status. Parodontal lysis is a late feature responsible for loosening of the teeth and, potentially, loss of teeth. Sicca syndrome with parotid gland hypertrophy has been reported. Depression is far from uncommon. In patients with arthralgia, myalgia, sicca, and purpura, Sjögren’s syndrome [49] or vasculitis [6] may be considered. Bleeding may suggest a blood cell or clotting disorder.

7. Laboratory findings

Laboratory test abnormalities are nonspecific. A common finding is anemia, which may be hypochromic, normocytic, or macrocytic. Although bleeding may contribute to induce anemia, the main factor is concomitant iron and folic acid deficiency. Folic acid is found in the same foods as vitamin C and is required for iron absorption. Intravascular hemolysis may also cause anemia. Leukopenia is not infrequent. Serum cholesterol levels are often low and vary in lockstep with serum ascorbic acid levels. Hypoalbuminemia is a marker for malnutrition found in most patients with scurvy [19]. The definite diagnosis is achieved by determining the serum ascorbic acid level, although the result is more heavily dependent on the recent ascorbic acid intake than on the body pool. The normal range is 5–16 mg/l, and clinical symptoms occur when values fall below 2.5 mg/l. Serum ascorbic acid levels should be interpreted in the light of results of tests for inflammation. Ascorbic acid is transferred from the serum to the leukocytes during the inflammatory response, so that ascorbic acid levels decline in the serum and rise in the leukocytes, although the body pool remains unchanged [50]. Leukocyte ascorbic acid assays provide a more faithful indicator of the body pool but are not available on a routine basis.
Table 1
Recommended daily allowance of ascorbic acid [60]

<table>
<thead>
<tr>
<th>Population</th>
<th>mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>50</td>
</tr>
<tr>
<td>Children aged 1–3 years</td>
<td>60</td>
</tr>
<tr>
<td>Children aged 4–6 years</td>
<td>75</td>
</tr>
<tr>
<td>Children aged 7–9 years</td>
<td>90</td>
</tr>
<tr>
<td>Children aged 10–12 years</td>
<td>100</td>
</tr>
<tr>
<td>Adolescents aged 13–19 years</td>
<td>110</td>
</tr>
<tr>
<td>Adults aged 20–60 years</td>
<td>110</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>120</td>
</tr>
<tr>
<td>Breast-feeding mothers</td>
<td>130</td>
</tr>
<tr>
<td>Elderly individuals</td>
<td>120</td>
</tr>
<tr>
<td>Smokers</td>
<td>140</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>140</td>
</tr>
</tbody>
</table>

8. Outcome

The outcome may be unfavorable if the diagnosis is missed. Severe bleeding may occur, and deficiencies in cell-mediated immunity and phagocytosis produce a risk of severe infection. Seizures and cardiac abnormalities may occur. ST-segment and T-wave changes are not infrequent, and sudden death has been reported [51]. During the 2003 war in Afghanistan, the World Health Organization identified 40 cases of fatal scurvy in the Taiwara area alone [52]. Vitamin C depletion (serum levels in the 2–5 mg/l range) does not consistently result in scurvy but may increase the risk of myocardial infarction [53] and severe infection [54,55]. In addition, the decreased antioxidant capabilities associated with vitamin C depletion may increase the risk of cancer [56], cataract [57], and death among males [58].

9. Treatment

Supplementation with 1 g/day of oral vitamin C for 2 weeks is the usual treatment. Divided doses distributed throughout the day should be used, as the intestinal absorption (and renal excretion) mechanisms become saturated with intakes greater than 100 mg. Parenteral administration is required in patients with malabsorption. The bleeding stops within 48 h, and an overall improvement is noticeable within 2 weeks.

A balanced diet that provides a large amount of fresh fruit and vegetables is sufficient to prevent scurvy. The recommended daily allowance for adults was increased in 1999 from 60 to 110 mg/day in France [59] and 120 mg/day in the United States [13]. These recommendations seek not only to prevent scurvy, but also to obtain plasma levels of ascorbic acid within the range (9–12 mg/l) that decreases the risk of cardiovascular disease, cancer, and cataract. Vitamin C requirements vary with age and patient-related factors (Table 1).

10. Conclusion

Scurvy selectively affects the homeless, the poor, and the elderly. Other risk factors include chronic and wasting diseases, intentional dietary restrictions, and lack of education about dietary needs. The musculoskeletal and other clinical manifestations may be misleading, particularly as few physicians in industrialized countries have first-hand knowledge of scurvy. An early diagnosis is vital, as the specific treatment is simple, inexpensive, and effective in eliminating the symptoms.

References


[36] Barlow T. On cases described as “acute rickets” which are probably a combination of scurvy and rickets, the scurvy being an essential, and rickets a variable, element. Med Chir Trans (London) 1883:66:159–220.


