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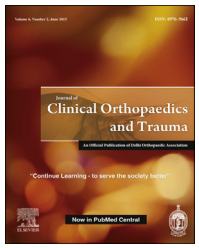

Review Article

Scurvy in pediatric age group – A disease often forgotten?

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ABSTRACT

Scurvy is caused by prolonged severe dietary deficiency of vitamin C. Being rare as compared to other nutritional deficiencies, it is seldom suspected and this frequently leads to delayed recognition of this disorder. Children with abnormal dietary habits, mental illness or physical disabilities are prone to develop this disease. The disease spectrum of scurvy is quite varied and includes dermatological, dental, bone and systemic manifestations. Subperiosteal hematoma, ring epiphysis, metaphyseal white line and rarefaction zone along with epiphyseal slips are common radiological findings. High index of suspicion, detailed history and bilateral limb radiographs aids physician in diagnosing this eternal masquerader. We searched Pubmed for recent literature (2009–2014) with search terms "scurvy" "vitamin C deficiency" "ascorbic acid deficiency" "scurvy and children" "scurvy and pediatric age group". There were a total of 36 articles relevant to pediatric scurvy in children (7 reviews and 29 case reports) which were retrieved. The review briefly recapitulates the role of vitamin C, the various disease manifestations and the treatment of scurvy to create awareness of the disease which still is reported from our country, although sporadically. The recent advances related to scurvy and its management in pediatric age group are also incorporated.

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1. Introduction

Scurvy is a disease caused by chronic deficiency of vitamin C. Being rare as compared to other nutritional deficiencies, it is seldom suspected and this frequently leads to delayed recognition of this disorder.[1,2] Its early diagnosis and appropriate treatment generally has gratifying results. We briefly review the role of vitamin C, the various disease manifestations and the treatment of scurvy to create awareness of the disease which still is reported from our country although sporadically.

1.1. Vitamin C and its role in body

Vitamin C (L-ascorbic acid or ascorbate) is an essential nutrient for humans and intimately concerned in the maintenance of intercellular connective tissues, osteoid, dentine and collagen.[3] Vitamin C plays an important role as a cofactor, enzyme complement, co-substrate, reducing agent and an antioxidant in several biochemical reactions.[4–6] It is essential for formation and stabilization of collagen triple helix, conversion of folic acid to folinic acid, synthesis of dopamine, norepinephrine, epinephrine and carnitine and metabolism of cyclic nucleotides and prostaglandins in human beings.[4,5] Vitamin C has potential antioxidant properties and stabilize a number of other compounds, including vitamin E and folic acid.[5] Iron absorption is enhanced as it is reduced to more absorbable ferrous state by vitamin C.[7] It may regulate inflammatory response by playing a role in metabolism of prostaglandins, adrenal steroids and catecholmines.[5] Human beings lack the enzymatic process for conversion of glucose to ascorbic acid via gulonolactone oxidase unlike other animals (e.g. rats), therefore vitamin C supplementation in the form of fresh fruits, vegetables, or dietary supplements is essential for humans.[7]

1.2. Dietary needs and sources of vitamin C

Vitamin C being water soluble is completely absorbed from gastrointestinal tract and gets widely distributed in both intracellular and extracellular tissues. The excess is excreted in urine. The recommended daily allowance (RDA) of vitamin C is 15–45 mg for age 1–13 years and 65–75 mg for age 14–18 years.[8] The requirement for vitamin C is increased during infections inflammatory states, pregnancy and lactation.[8]

The new born infant vitamin C level are related to the maternal levels as the vitamin is transported by active placental transfer and subsequently maintained by secretion of vitamin C in breast milk or commercial infant formulas.[8] Best sources of vitamin C are citrus fruits (e.g. oranges, lemons, limes, grapefruits, gooseberry, black currents, melons) and vegetables (e.g. tomato, potatoes, green chilies, cabbage, broccoli, spinach, lettuce, cucumber, Brussels sprouts, red peppers).[7] Human milk is richer in vitamin C than cow's milk. Many foods can lose their vitamin C content because of cooking, storage, or oxidation. There is practically no storage in the human body. Plasma concentration is related to daily intake. However, some tissues do carry higher concentrations (e.g. white blood cells, adrenal glands, pituitary gland).[8]

1.3. Deficiency of vitamin C

A deficiency of vitamin C results in the clinical presentation of scurvy, the oldest recognized nutritional deficiency disease.[5] Conditions similar to scurvy were known to ancient Egyptians.[9] English sailors knew that the disease could be prevented by taking fresh lime.[10,11] However in 1753, the entity came to be known as scurvy and its prevention by citrus fruits was described by Sir James Lind, and ascorbic acid was first isolated in 1928.[10,11] Scurvy is a rare disease in current era. Scurvy in pediatric age group is scantly reported when compared to certain adult groups (e.g. uncared elderly living alone, alcoholics, food faddists, suffering for psychiatric disorders).[7] Infants at risk include those who are fed evaporated or boiled milk, exclusive meat feeding and children with dietary restrictions due to neuropsychiatric or developmental disorders.[7,12–14] Someother medical conditions can also reduce the absorption of vitamin C and/or increase its amount needed by the body. Children with intestinal malabsorption syndromes and some cancer patients might be at increased risk of vitamin C inadequacy.[12] Low vitamin C concentrations can also occur in patients with end-stage renal disease undergoing chronic hemodialysis or on ketogenic diet sometimes recommended for controlling refractory status epilepticus.[13,15]

1.4. Clinical features of scurvy

Even 8–12 weeks of irregular or inadequate intake of vitamin C can result in clinical symptoms.[5] The initial manifestations are non-specific such as irritability, loss of appetite, low grade fever and later dermatological such as petechiae, ecchymoses, hyperkeratosis and cork screw hairs.[16] The capillaries are fragile and there is a tendency to hemorrhage. Recently, reduced thrombocyte aggregation and platelet dysfunction attributable to scurvy is postulated to contribute to the hemorrhagic diathesis.[17] Gums become swollen, loosen and bleed on slightest pressure (Fig. 1). Gingival disease manifestation in children is due to poor dentine formation resulting in poor teeth formation. Bone changes usually follow clinical changes however, bone disease can be the more frequent presentation bringing the child to medical attention (Fig. 2).[7,8] Bone involvement in scurvy is typically symmetrical.[18,19]

Deficiency of vitamin C results in a poor formation of the bone osteoid causing disruption in enchondral bone formation.[18] Mineralization generally remains undisturbed and therefore the provisional zone of calcified cartilage becomes excessively calcified. However, because the osteiodis defective and deficient, the bones become brittle and readily fracture.[19] This leads to skeletal manifestations of scurvy. Early manifestations mentioned above are followed by leg swelling (mostly marked at the knees and the ankles). Hemorrhages occurring beneath the periosteum and into the joints and fractures around growth plate cause extreme bone and joints pains. Slipping of epiphysis around major joints has been reported (Fig. 4).[7,18,20] The infant may have features of pseudoparalysis[21] and the presentation may have posture of "pithed

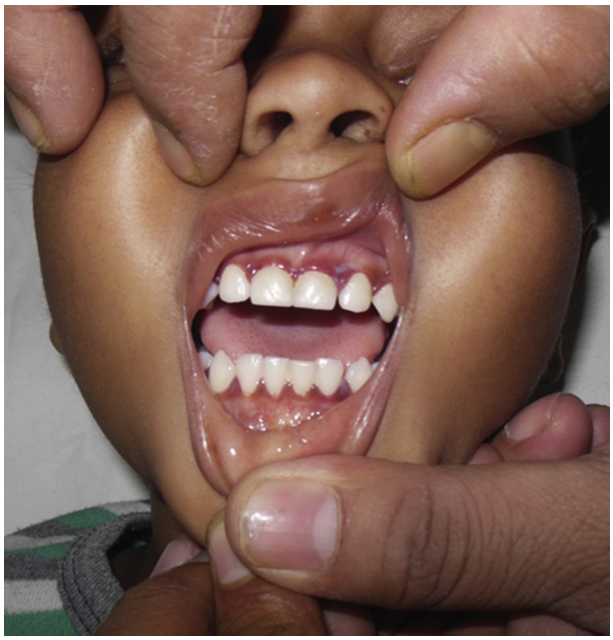

Fig. 1 – Clinical photograph showing inflammed marginal gingiva in scurvy.

frog" (a stunned position of animal after its brain is destroyed) (Fig. 3a and b), with the hips and knee semiflexed.[8] The child is frequently irritable and does not like handling. A "scorbutic rosary" at the costochondral junctions and sternum depression are other characteristic bony features.[8]

Anemia is another hallmark of scurvy. Iron deficiency anemia is common and may be secondary to a combination of bleeding, and decreased absorption.[7] Hemorrhagic manifestations of scurvy include petechiae, purpura and ecchymoses at pressure points, epistaxis, and the characteristic perifollicular haemorrhages.[8]

Different clinical manifestations in spectrum of scurvy are reported recently especially in non-ambulatory children and toddlers. Cain et al described a toddler who presented with leg weakness and a petechial rash due to severe ascorbic acid deficiency.[22] Another presentation in young children is difficult walking.[23–25] It is also suggested to keep scurvy in differential diagnosis of arthralgia, myalgia and arthritis in pediatric patients with restricted diet/autism or developmental delay.[26–28] Proptosis due to orbital hemorrhage can also be one of the presentations of scurvy.[29] Other rare clinical signs of scurvy include skeletal muscle degeneration, complex regional pain syndrome (CRPS), cardiac hypertrophy, pulmonary hypertension, diminished adrenal and bone marrow function, psychological changes, poor postoperative wound healing, edema, and alopecia. Untreated scurvy can lead to disruption of metabolic processes in body and can be fatal, with deaths reported from infection, cerebral hemorrhage, or hemopericardium.[7,30,31]

1.5. *Radiological findings of scurvy*

The typical radiographic changes occurs at the distal ends of the long bones and are particularly common at the knees and ankle.[8] The most common radiographic finding although nonspecific is osteopenia.[7] A deficient osteoid matrix and loss of trabeculae project a "ground glass" roentgenographic appearance.[32] Brittle and fragile bones fracture easily (including Salter-Harris I fractures of the distal femur), and often heal with abundant callus formation.[32] The bone cortex is thin and sharply contrasted when compared to medullary region giving the appearance of pencil outlining of the diaphysis and epiphysis. An irregular but thickened white line appears at the metaphysis (White line of Fraenkel) (Figs. 5 and 6), representing the zone of well-calcified cartilage.[33] The more definite but late specific radiological feature of scurvy is a zone of rarefaction beneath Frankelline in the metaphysis (secondary to poorly formed trabeculae) known as the Trümmerfeld (German word for "field of rubble") zone.[34] Another finding associated with healing fractures of the Trümmerfeld zone is the "beaks", also known as Pelkan spurs (Fig. 6) found at the periphery of the zone of metaphyseal calcification. They are associated with periosteal elevation and may be produced by lateral growth of the calcification zone.[7] A circular, opaque shadow in the growth centers is

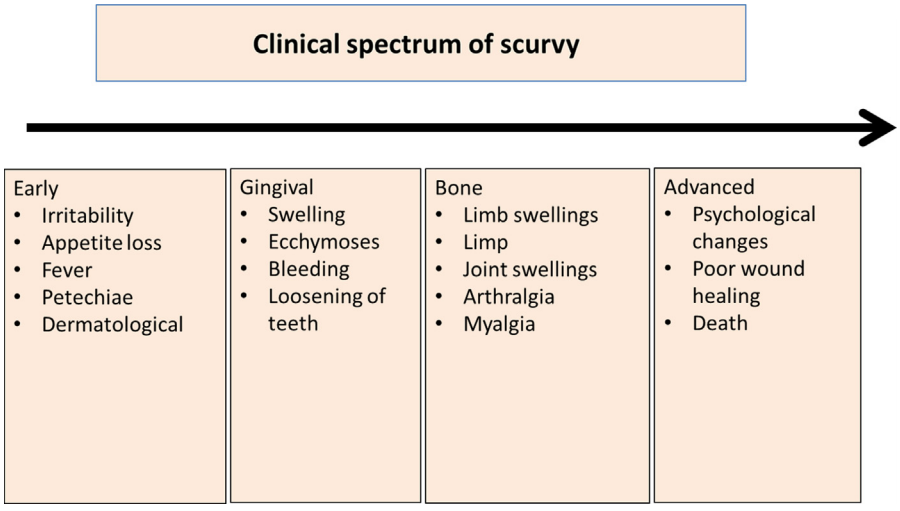

Fig. 2 – Clinical spectrum of scurvy is discrete and patients can presented with isolated clinical findings.

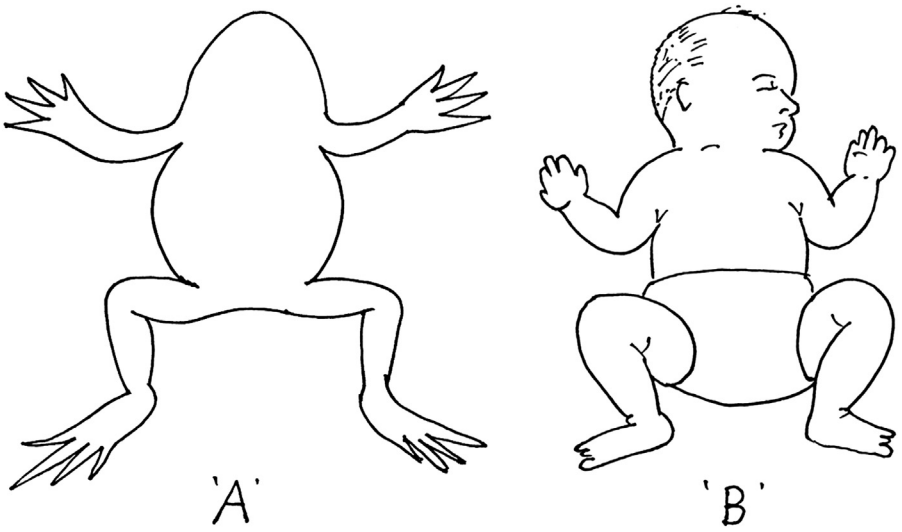

Fig. 3 – Drawing showing (A) pithed frog, (B) child in pithed frog posture.

often surrounded by a white line around the epiphysis, known as Wimberger ring sign.[34] Paraepiphyseal subperiosteal hemorrhages (Fig. 4) are visualized only during the healing phase of scurvy.[7] A deficient collagen, the structurally weak bone with reduced capacity to handle weight-bearing stresses or strong muscular tension may produce physiolysis and epiphyseal separations.[18]

1.6. *Diagnosis of scurvy*

A useful mnemonic for remembering many of the common presentations of scurvy is **4 *"H"*: h**emorrhagic signs, **h**yperkeratosis, **h**ematologic abnormalities, and **h**ypochondriasis (*delusion of being sick*).[7] With a presentation similar to osteomyelitis[35] or abscess, aspiration is frequently performed in a mistaken diagnosis and in such cases the aspirate yield is hemorrhagic fluid. Another common differential is tumorous growth (See Table 1).[36] A thorough clinical history and examination followed by radiographs can help arrive at scurvy diagnosis. As mentioned earlier, scurvy has a spectrum of clinical features and presence of isolated/noncontiguous symptoms may cause confusion for unwary. Cases are on record when the child was otherwise healthy and disease's oral manifestations led to the diagnosis.[36–38] Thus the disease can easily be misdiagnosed/missed.

A low plasma level of vitamin C (plasma ascorbate concentration of <0.2 mg/dl usually is considered deficient) is specific in scurvy. However, the levels may be normal if there has been recent vitamin C supplementation in any form. Thus determination of plasma vitamin C levels remains an

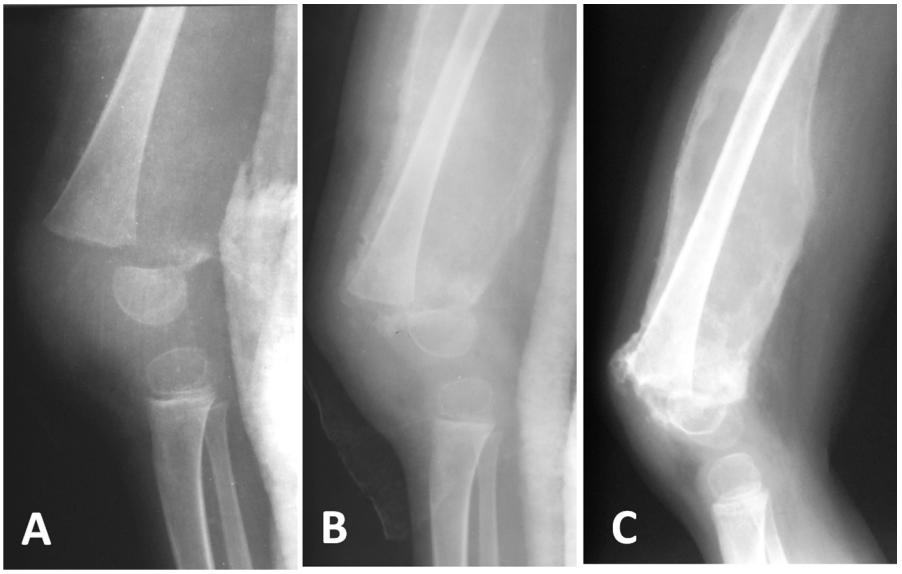

Fig. 4 – Radiographs of right thigh showing (A) lower femoral epiphyseal slip. Subperiosteal hematoma was not visible initially, (B) subperiosteal hematoma (in healing stage) after treatment was initiated, (C) final radiographs after completion of treatment.

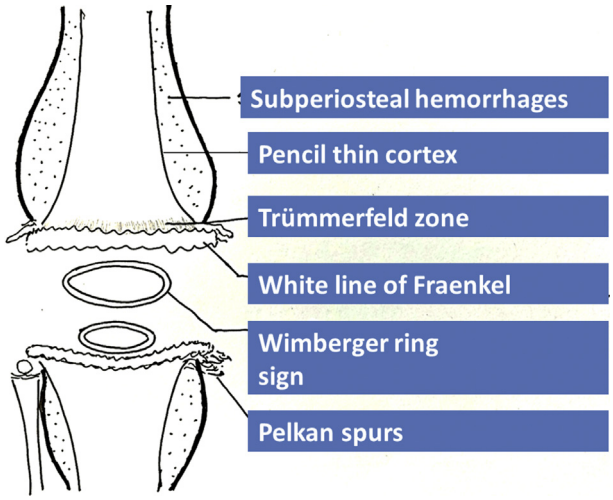

Fig. 5 – Drawing showing radiological signs in scurvy.

insensitive laboratory test for vitamin C deficiency.[8] Measuring the vitamin C level in the buffy-coat of the leucocytes is a better estimate of the vitamin body stores. However, this method is technically demanding and not available freely.[7] Leukocyte concentrations of less than or equal to 10 μg/10^8 WBCs are considered deficient and indicate latent scurvy.[8] Another indicator of vitamin C body stores is its measure of urinary excretion after parenteral ascorbic acid infusion. After 100 mg of an intravenous dose of vitamin C, 80% should be excreted within 5 h if the body stores are not deficient.[7]

In practice, the diagnosis of scurvy is based on a combination of clinical and radiographic findings. Scurvy can be the differential diagnosis when a dietary history indicates insufficient intake of vitamin C for at least 1–3 months and related clinical signs and symptoms are present.[39] In cases of suspicion, therapeutic test wherein resolution of the disease manifestations occur after vitamin C supplementation remains the best evidence.[7,40]

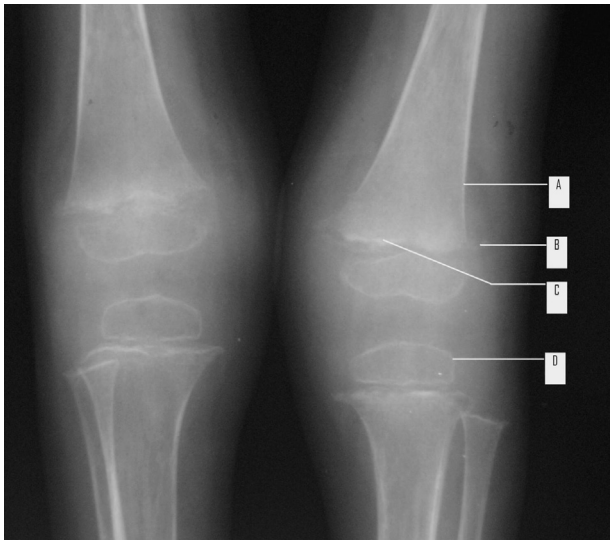

Fig. 6 – Radiographs of the both knee showing (A) pencil thin cortex, (B) pelkan spurs, (C) Fraenkel line, (D) ring epiphysis. The radiographs show a washed out appearance.

Unexplained acquired thrombocytopathy should also be investigated for possible scurvy.[17] Vitamin C deficiency may occur concurrently with other nutritional deficiencies such as thiamine (vitamin B1), pyridoxine (vitamin B6), cobalamin (vitamin B12), and vitamin D and this should be kept in mind while investigating scurvy.[30] A nanoprobe for detection and imaging of ascorbic acid in living cells and in vivo based on the specific reaction of cobalt oxyhydroxide and ascorbic acid has been proposed and currently experimentally investigated.[41]

The plain radiological findings in scurvy are already been described above. Ultrasound may reveal bony irregularity, bulky subcutaneous plane, intramedullary or periosteal mass, subperiosteal hemorrhagic collections. MRI is usually done because of the simulating malignancy features, especially leukemia.[7] MRI findings in scurvy will reflect the underlying pathophysiology, with areas of hemorrhage seen within bones at the site of fracture and in the periosteum and the diffuse marrow changes typically seen in hematological malignancies such as leukemia will be absent.[26] Further there will be multifocal symmetrical signal abnormalities involving the metaphyses with associated marrow enhancements.

2. Treatment

Infants and children are usually treated with vitamin C 100–300 mg daily and adults 500–1000 mg daily for 1 month or until full recovery of clinical signs and symptoms occurs. Spontaneous bleeding as well as oral and constitutional symptoms are the foremost to recover (in days) while bone abnormalities and ecchymoses resolution take longer (in weeks).[7,42] Along with vitamin C therapy, symptomatic treatment should also be given in the form of analgesics and rest to the part through splintage. There is no role of antibiotics in the management of such patients.

Separation of the epiphysis from the metaphysis is always through the zone of provisional calcification, the weak zone. With occurrence of this fracture, periosteum stripping occurs with collection of subperiosteal hematoma. Following nutritional supplementation vitamin C, this subperiosteal hematoma quickly calcifies. Two phenomenon occur: new bone is laid beneath the elevated periosteal sleeve and the underlying protruding shaft undergoes rapid resorption and get aligned with long axis of bone. After subperiosteal bone formation, the epiphysis becomes centered on the widened metaphyses.[20,43] Separation of the epiphysis in scurvy is best treated conservatively by splintage and vitamin C supplementation and a closed or open surgical reduction of the displace depiphysis is rarely required. Complete remodeling follows in a child and residual deformity or growth disturbance are seldom reported.[43]

3. Conclusions

Although a rare disease, scurvy is reported more commonly from developing countries where malnutrition is quite

Table 1 – Common differential diagnosis of scurvy.[20,35,36]

1. Osteomyelitis
2. Septic arthritis
3. Child abuse and neglect
4. Hematological and soft tissue malignancies (e.g. acute lymphoblastic leukemia)
5. Autoimmune diseases (e.g. Henoch-Schönleinpurpura, systemic lupus erythematosus, Sjogren syndrome)
6. Vitamin D deficiency and related disorders
7. Disseminated intravascular coagulation
8. Platelet dysfunction (e.g. immune thrombocytopenic purpura)
9. Senile purpura
10. Thrombophlebitis, deep venous thrombosis
11. Meningococcemia, rocky mountain spotted fever
12. Hypersensitivity vasculitis (leukocytoclastic vasculitis)
13. Necrotizing gingivitis
14. Pediatric syphilis
15. Functional syndromes and neuropsychiatric disorders

prevalent. As scurvy can present itself in various forms and can mimic presentation of a number of common diseases, a high index of suspicion is required with stress on detailed clinical history including dietary history and comparative bilateral radiographs so that this disease could be diagnosed and treated.

Conflicts of interest

All authors have none to declare.

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