

Reply to Editor

Could Vitamin C deficiency have a role in shaken baby syndrome?

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Unexplained subdural hematoma in infants, with or without retinal hemorrhages and skeletal fracture, has been considered by some to be pathognomic for non-accidental injury (Fig. 1). However, there is increasing concern that the exact pathogenesis of these findings is not well understood. Dr Clemeston has proposed that some of these cases of presumed shaken baby syndrome (SBS) were due to vitamin C deficiency, and has recommended that plasma ascorbic acid and whole blood histamine should be included in the diagnostic workup of all cases of suspected SBS.¹

Vitamin C deficiency was common in the 19th century and early 20th century. It typically presented with non-specific symptoms of listlessness, loss of appetite, irritability and failure to thrive. Affected children could have tender extremities, which may or may not be swollen as a result of subperiosteal hemorrhages. In advanced cases, a scorbutic rosary is present. Purpura or petechiae may be observed over the skin. Gum swelling may not be obvious initially and a more general bleeding diathesis has also been reported.

A literature review was undertaken to search for potential evidence of a relationship between vitamin C deficiency and SBS. Ovid Medline was searched for publications using 'vitamin C' and/or 'ascorbic acid' as the keyword for the years 1966–2003. Index Medicus was searched for pre-Medline publications up to the year 1946. Only English literature was included Table 1.

Vitamin C has a wide range of physiological functions inside the human body. Ascorbic acid is a required cofactor of the prolyl hydroxylase in the hydroxylation of prolyl residues in the synthesis of collagen. Vitamin C deficiency can result in vascular fragility by formation of defective collagen in the vessel basement membrane, leading to a tendency to bleed. Subperiosteal and subcutaneous hemorrhages are the most commonly reported complications. Rare complications include intra-articular, and orbital hemorrhages. The clotting profile usually remains normal, as the clotting factors

are not affected. The Hess test is suggested to document capillary fragility but this test is not specific to vitamin C deficiency.² Despite the biological plausibility, no case of subdural hematoma with documented vitamin C deficiency was found in the literature reviewed.

Subperiosteal hemorrhages and dysfunction of osteoblasts can cause skeletal changes in patients with scurvy.³ The former can present with painful swellings of the ankles/knees or 'pseudoparalysis'. The costochondral junctions may be prominent, forming a rosary from subluxation of the sternum, unlike the ricketic rosary where the rib ends are expanded. Radiological changes in scurvy include: (i) characteristic dense line of provisional calcification at the metaphysis (Fraenkel's line); (ii) ground-glass appearance of bone due to atrophic spongiosis; (iii) pencil outline or a ringed white margin of the epiphysis due to thickened peripheral shell of calcification; (iv) fissure and fractures; (v) lateral spurs; (vi) subperiosteal hemorrhages; and (vii) transverse band (scurvy line) of atrophic bone layer between the sclerotic provisional zone and the spongiosis in the shaft.³ It is well recognized that scurvy is one of the differential diagnoses of the healing classical metaphyseal lesions in infants suffering from physical abuse.⁴ But rib fractures are often considered to be diagnostic of child abuse and are rarely seen in accidental injury. They are only occasionally seen in severe forms of osteogenesis imperfecta, metabolic bone disease and in premature infants.⁴ However, tendency to bleed and subdural hematoma are not associated with osteogenesis imperfecta and metabolic bone disease.

The actual incidence of SBS is not well established, and whether the incidence varies significantly by country or region remains to be determined. The National Center on Shaken Baby Syndrome in the United States estimates that the incidence of SBS ranges from 600 to 1400 cases per year. Vitamin C deficiency is believed to be extremely rare in industrialized countries, except in high-risk populations such as the elderly or children with psychomotor retardation. It occurs most commonly between 5 and 24 months of age, with peak incidence between 8 and 11 months. Its occurrence varies according to standard weaning practice and the methods of food preparation, because Vitamin C is destroyed after cooking. These factors also change with time. No reports of large-scale studies assessing the incidence of vitamin C

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Table 1 Search strategy

Key words 'vitamin c'/'ascorbic acid' yielded 11952 articles. The authors reviewed titles and abstracts of possibly related articles (hundreds), and identified and read the original articles of those deemed most relevant (approximately 50 papers)
Key words 'vitamin C' combined with 'haemorrhage', 'cerebral hemorrhage', or 'subdural hemorrhage' (27838 articles) yielded 23 relevant articles
Key words 'vitamin C' combined with 'fracture', 'skull fracture', 'humerus fracture' (44032 articles) yielded 25 articles

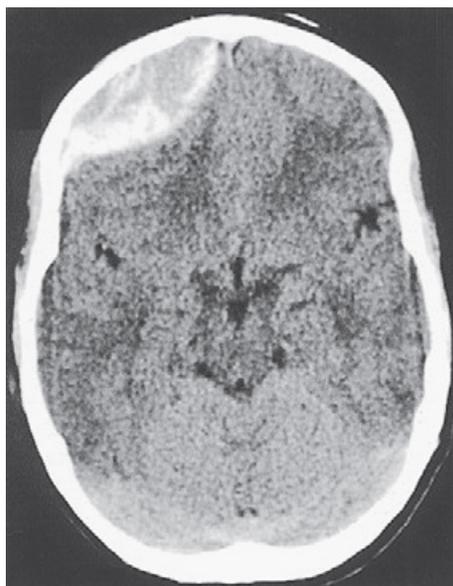


Fig. 1 Acute subdural hematoma over right frontal region with some pressure effect.

deficiency in healthy infants in developed countries during the past 20 years were identified.

Another issue complicating the documentation of vitamin C deficiency is the variety of biochemical methods used to measure vitamin C status in humans. This may be a factor that has contributed to the paucity of studies on vitamin C status in healthy infants. There are two forms of ascorbic acid: ascorbate and dehydroascorbate (the oxidized form). Lee *et al.* found that less than 5% of the total ascorbic acid in plasma was present as dehydroascorbic acid.⁵ The presence of dehydroascorbic acid in plasma is controversial since it is not always present. Thus many scientists believe that measurement of ascorbate concentrations in plasma/serum is already adequate to reflect the vitamin C status. However ascorbic acid levels decline when specimens are held at room temperature, so metaphosphoric acid has been used to stabilize samples, and refrigeration is required for storage of specimens. Among the numerous methods described, high performance liquid chromatography (HPLC) is the method of choice to measure the vitamin C components in blood. The World Health Organization has published recommended procedures to assay vitamin C.⁶ However, which blood

component is the best to document vitamin C status in humans remains controversial. Plasma or serum ascorbic acid concentrations are considered to be more reflective of recent intake of ascorbic acid than of body stores, while blood leukocyte ascorbic acid concentrations are more reflective of tissue stores of ascorbic acid. However measurement of the latter is more tedious to perform. Low serum concentrations of ascorbic acid (<0.3 mg/dL) do indicate low or inadequate intake of vitamin with only partial reserves present. Thus serum (plasma) ascorbic acid analysis is considered the most feasible procedure for evaluating vitamin C status.⁶

Recent studies have shown that ascorbic acid levels are significantly inversely correlated to the severity of neurological impairment (as assessed by the Glasgow Coma Scale and National Institute of Health Stroke Scale) in patients with head trauma and hemorrhagic stroke of acute onset.⁷ Leukocyte vitamin C levels have also been reported to show a transient decrease during acute phase response.⁸ This may have implications in interpretation of plasma ascorbic acid concentrations in SBS. Do the low levels imply a state of deficiency or merely reflect a transient response to stress or head injury? Most of the patients are acutely sick upon presentation and they may be kept fasting during the initial few days of hospital care. Will the blood samples taken after several days of fasting have falsely low concentrations of vitamin C?

Some patients with severe subdural hematomas may not survive the initial resuscitation and surgical intervention. Thus, without the characteristic autopsy findings of severe scurvy, it may be difficult to demonstrate biochemical vitamin C deficiency in such cases. Allender has attempted to analyze levels of vitamin C in autopsy samples using a sensitive amino-bonded reverse-phase high-performance liquid chromatography technique,⁹ but more information on the assessment of the vitamin C status in postmortem studies is required.

Histamine has been found to have an inverse relationship with plasma ascorbic acid level.¹⁰ Johnston *et al.* found that blood histamine and plasma free carnitine are altered in individuals with subnormal, non-scorbutic vitamin C status and they proposed that these measures be used to formulate optimal intake of vitamin C. However it appears that there are still no well-accepted functional assays for vitamin C status and histamine levels cannot be taken directly as a reflection of vitamin C status.⁶

From the available information in the literature, there is no convincing evidence to conclude that vitamin C deficiency can be considered to be a cause of SBS. Although vitamin C deficiency could explain some of the signs and symptoms of SBS more research is required to try to prove or disprove this hypothesis. As with many hypotheses, obtaining this proof may be extremely difficult to do in practice. Establishing the extent to which subclinical vitamin C exists in infant populations could be an important starting point. Determining whether there are measures of subclinical vitamin C deficiency that can be reliably measured post-mortem would be necessary to determine whether a relationship exists between this deficiency and SBS. More consensus is required to standardize the measurement of ascorbic acid in different laboratories. Further information regarding the influence of acute stress and head injury on the concentrations of ascorbic acid and the validity of post mortem vitamin C levels in documenting a deficiency state will be required before the possible relationship between vitamin C deficiency and SBS can be evaluated.

In the meantime we need to continue to keep an open mind in investigating cases of suspected SBS. Differential diagnoses such as coagulopathies, osteogenesis imperfecta, infection, and metabolic disease should always be considered, especially when the presentation is atypical. We need to look at other evidence and consider the history, physical findings and investigation results as a whole, and be extremely cautious in drawing conclusions about causation.

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