Is it "Shaken Baby," or Barlow's Disease Variant?

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ABSTRACT

Retinal petechiae, subdural hemorrhages, and even broken bones do not always indicate trauma or child abuse. Infantile scurvy or a variant form still occurs today and can be mistakenly diagnosed as nonaccidental injury (NAI). Histamine levels, which are characteristically increased in vitamin C depletion, may reach a toxic level owing to infection or the injection of foreign proteins. Histamine intoxication can cause a variant of Barlow's disease, with weakness of the retinal vessels and the bridging veins and venules between the brain and the dura mater in infants.

In the first 75 years of the 20th century, Barlow's disease–with bruises, broken bones, and sores that would not heal–was a well-recognized condition in the Western world, affecting bottle-fed infants whose mothers did not know or could not afford to provide orange juice as a supplement to the milk diet. Scurvy also occurred in the infants of more affluent mothers who boiled cow's milk to be sure of destroying all tuberculosis bacteria. The heat of boiling destroyed the vitamin C.

In the early papers describing shaken baby syndrome, both Caffey[1] and Kempe[2] refer to the possibility of infantile scurvy, or vitamin C deficiency, in the cases cited in the series they reported as battered children. This seems to have been forgotten by their followers. Today the diagnosis may be missed partly because of the belief that vitamin C deficiency could not possibly occur in our modern world. It certainly does in adults, as shown by Johnston and Thompson.[3] Clinical diagnosis is difficult in edentulous infants because they never show the sponginess or bleeding of the gums so typical of adult scurvy. Laboratory analysis for plasma ascorbic acid or blood histamine levels is seldom done before making the diagnosis of "shaken baby syndrome."

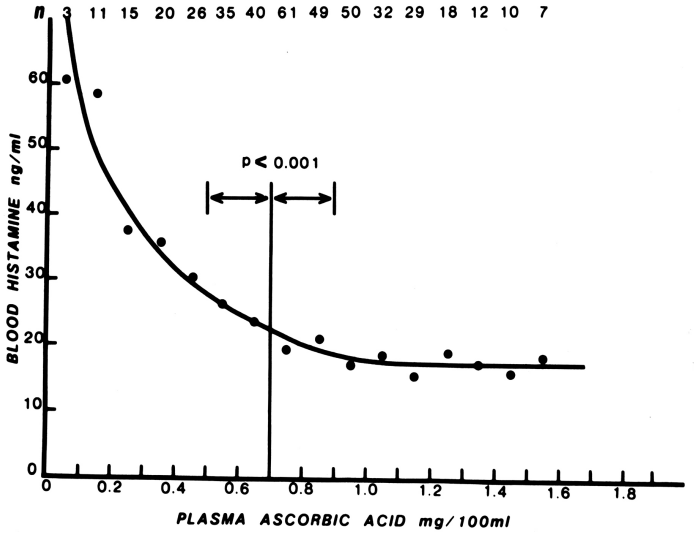

Figure 1. Results of plasma ascorbic acid (reduced form) and whole blood histamine concentrations in the same blood samples from 437 human volunteers in Brooklyn, NY (1980). A highly significant increase in the blood histamine level was evident when the plasma ascorbic acid level fell below 0.7 mg/100 mL. This comprised 150 of the 437, or 34 percent, of the men and women. Data from Clemetson.[6]

Inadequate dietary intake is only one of many factors leading to Barlow's disease. Wounds and infections can also cause vitamin C depletion, as can trauma, surgery, cigarette smoke, hemolysis, heavy metals, and many drugs such as fenfluramine.[4]

The Role of Histamine

We now know that capillary fragility, so characteristic of scurvy, is the result of elevated blood histamine levels, which occur with even mild ascorbate depletion, as shown both in guinea pigs[5] and in human subjects[6] (Figure 1). There is no change in the blood coagulation mechanism in the histamine intoxication of uncomplicated scurvy. Similarly, Fung et al., in 2002,[7] found no abnormality in the blood coagulation studies carried out on nine infants with retinal and subdural hemorrhages. They had been diagnosed as NAI, or nonaccidental injury, even though there was no suspicion of child abuse. These authors suggest that the prevailing view that unexplained subdural hematoma and retinal hemorrhages are pathognomonic for child abuse is "a self-fulfilling prophecy." It certainly seems to have become a self-propagating assumption. We need to consider not only ascorbate depletion, but also all the other factors that can affect blood histamine levels and so contribute to the development of a variant of Barlow's disease.

No one disputes the defect of collagen synthesis in scurvy, but that alone could not account for the bleeding, as there is very little fibrous tissue surrounding the endothelium of the capillaries and venules from which scorbutic bleeding occurs. There is, however, a widening of the intercellular spaces between the vascular endothelial cells in scurvy[8] (Figure 2), and following histamine injection[9] (Figure 3).

Many factors, including injection of foreign proteins, can cause histaminemia, as shown in guinea pigs by Chatterjee et al.[10] Even lack of sleep more than doubles the blood histamine concentration in resident physicians after a day and a night on duty ($p < 0.001$).[4] L-ascorbic acid is needed to facilitate removal of histamine by conversion to hydantoin-5-acetic acid, and on to aspartic acid in vivo.[10] Even a mild reduction of the plasma ascorbic acid level,

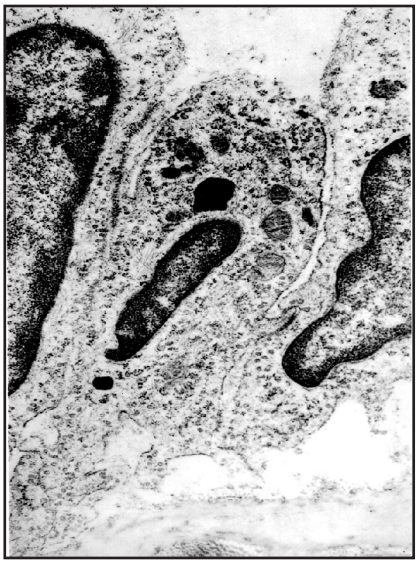

Figure 2. Electron micrograph of scorbutic guinea pig aortic endothelium: Note the widened intercellular junction gaps. From Gore et al.,[8] with permission from the AMA.

below 0.7 mg/100 mL (39.8 μ mol/L) in human subjects, causes a highly significant increase in the blood histamine concentration (Figure 1).

Clearly, histaminemia from any cause will be added to the histaminemia of ascorbate depletion and could cause subdural hemorrhages, retinal petechiae, and bruising elsewhere–so easily mistaken for child abuse. The resultant extravasations of blood will lead to extravascular hemolysis and jaundice; hemolysis leads to further ascorbate depletion[4] and may destroy any residual traces of ascorbic acid. If this process continues for any length of time, frank scurvy with subperiosteal hemorrhages, epiphysial separations, and bone fractures can develop.

Infant Feeding Practices

Today, it is the fashion to give bottle-fed infants supplementary apple juice instead of orange juice, but apples are a poor substitute for oranges. One hundred grams of fresh orange juice (3¼ fluid ounces) contains about 49 mg of vitamin C, but the same amount of apple juice contains only 1 mg of this vitamin. So, unless the parent knows to buy apple juice with added vitamin C, there can still be a risk of vitamin C deficiency. Likewise, we may suppose that there could be a problem if someone were to overdo any heating of the baby's bottle in a microwave oven.

Maternal Factors

The probability of Barlow's disease can be increased by maternal malnutrition, by hyperemesis gravidarum (excessive vomiting in pregnancy), and by bacterial or viral infections in the mother or the infant. In 1943 Lund and Kimble[11] reported: "Hyperemesis gravidarum may lead to dangerously low levels of vitamin C. Clinical scurvy may appear. The retinal hemorrhages of severe hyperemesis gravidarum are a manifestation of vitamin C deficiency and are similar to petechial hemorrhages seen elsewhere. The hemorrhages cease after adequate therapy with vitamin C; henceforth they are not necessarily an indication for the use of therapeutic abortion."

Whenever a woman complains of excessive vomiting in pregnancy and is found to have acetone or acetoacetic acid in the urine due to starvation, even for a day or two, she should be admitted to hospital and given intravenous fluids and supplementary vitamins. For some reason, vitamin C deficiency develops very rapidly in hyperemesis gravidarum. Retinal hemorrhages and jaundice used to be indications for therapeutic abortion to prevent the development of Wernicke's encephalopathy, with hemorrhages in the corpora mammilaria and neighboring structures of the maternal brain.

Infant Inoculations

Individual reactions following inoculations, or vaccinations, are highly variable, both in timing and severity, as shown by Buttram.[12] Some infants die 10 to 20 days after multiple inoculations, and it is very difficult to determine whether there is a causal relationship in such cases.

Most physicians will not question that blood histamine levels can be increased by injection of foreign proteins into the body, but few physicians are aware that human blood histamine levels are inversely proportional to the plasma vitamin C concentration (Figure 1); nor are they aware that 6 percent of apparently healthy individuals are severely vitamin C-depleted.[1] Hospital laboratories do not yet conduct plasma ascorbic acid analyses as part of their routine work, even though ascorbate depletion is common following injury, surgery, or infection.

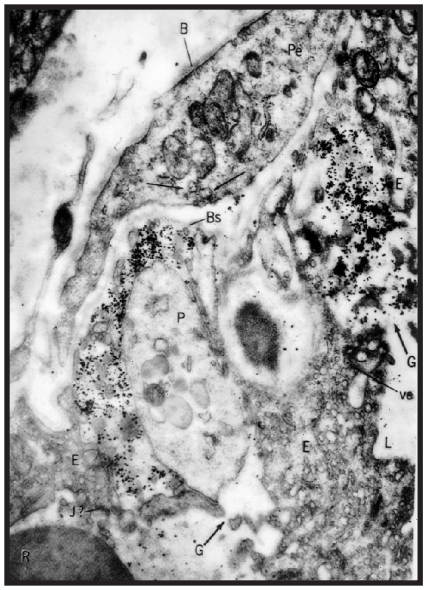

Figure 3. Electron micrograph of the wall of a leaking rat blood vessel, 2½ minutes after local injection of histamine and i.v. injection of HgS, which was used as a marker. Endothelial gaps are seen (G,G). Tracer particles, chilomicra and a platelet (P), have penetrated into the wall of the vessel. Bs septum arising from the basement membrane, Pe pericyte, E endothelial cell, L vascular lumen, B basement membrane, R red blood cell, ve a lone tracer particle within an endothelial cell, J ? intercellular junctions. From Majno and Palade,[9] with permission from Rockefeller Institute Press.

Not so long ago we gave infants one, two, or three inoculations at one time, but now infants often receive six inoculations together at eight weeks of age. This challenge may be too great for some infants with borderline vitamin C depletion due to an upper respiratory infection or other illness.

Anti-Toxic Effects of Vitamin C

Recent reviews of the world scientific literature[13,14] reveal that supplementary ascorbic acid (vitamin C) has a remarkable and highly significant protective effect against the morbidity and mortality resulting from the injection of the toxins or toxoids of diphtheria, typhoid, gas gangrene, and tetanus in animals. Moreover, the work of Kalokerinos[15] has shown the value of vitamin C as a life-saving agent following routine inoculations in human infants.

Other Causes of Subdural Hemorrhage

Prenatal ultrasound examinations have revealed the existence of unexplained subdural hemorrhages in utero.[16,17] Additionally, some newborn infants have been found to have subdural hemorrhages after normal delivery.[19] It is therefore clear that the strength of the bridging veins between the brain and the dura is quite variable.

Glutaric aciduria type 1 is well documented as a cause of retinal and subdural hemorrhage.[20] Hemorrhagic disease of the newborn, readily detected by coagulation studies, is another possibility.

Needed Research

To avoid taking too many blood samples from infants, researchers should preferably conduct studies on soldiers receiving their inoculations for overseas duty. The same blood samples should be analyzed for plasma ascorbic acid and for whole blood histamine, both before and at different intervals after single and multiple inoculations. We may anticipate that a greater blood histamine increase will occur in those with low ascorbic acid levels. Moreover, clinical investigators will be able to compare the timing and the extent of such histamine elevations after different single or multiple inoculations. Research on infants should follow.

Conclusions

The diagnosis of Barlow's disease has almost disappeared, while the frequency of a diagnosis of shaken-baby syndrome has increased in recent years. Unfortunately, many such infant deaths are wrongly attributed to shaken-baby syndrome, without any real evidence that the infant was shaken and without any consideration of Barlow's disease. As Donohoe recently remarked,[18] many studies of shaken-baby syndrome make the obvious logical error of selecting cases by the presence of the very clinical findings and test results they seek to validate as diagnostic. All other possible diagnoses must be considered.

No one should ever be accused of inflicting shaken-baby syndrome unless analyses for plasma ascorbic acid and blood histamine have been performed and can be placed in evidence. Undoubtedly, subdural hemorrhages due to capillary fragility led to the delayed development, epilepsy, and four cases of spastic quadriplegia among the nine cases of unexplained subdural hematoma reported by Fung et al.[7] We should not start by asking, "Was the baby shaken?" but rather, "Were the capillaries of the retina and venules of the bridging veins strong enough to withstand normal handling?" No one should ever be indicted unless there has been direct evidence of physical abuse.

To reduce the risk of Barlow's disease, we should consider the following: (1) Postponing inoculations for infants who are premature or ailing in any way, even with an upper respiratory infection; (2) reconsidering the wisdom of giving as many as six inoculants, all at once, to infants at eight weeks of age; and (3) administering 500 mg of vitamin C powder or crystals, in fruit juice, to infants before inoculation; and (4) giving an additional ascorbic acid by injection to any infant showing a severe reaction such as convulsions or a high-pitched cry.

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Disclosures: This article received no financial support, and no competing interests were disclosed.

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