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**CAPILLARY FRAGILITY AS A CAUSE OF
SUBDURAL HEMORRHAGE IN INFANTS**

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ABSTRACT. MALNUTRITION, EXCESSIVE VOMITING, surgery, or infection can cause a pregnant woman to develop a profound vitamin C deficiency and an excessive blood histamine level, leading to capillary and venular fragility. Sleep lack and other stresses in the mother can further elevate her blood histamine level and affect the unborn child, thus weakening the retinal capillaries and the bridging veins between the brain and the dura mater. Subdural hemorrhages in the infant have now been identified by ultrasound examination before birth and even before labor. Vaccines and toxoids have been shown to increase the blood histamine level of guinea pigs. We need to establish the blood histamine and ascorbic acid levels of human subjects before and after single and multiple inoculations. Undoubtedly, the histamine level will increase more in those having low ascorbic acid levels, and especially in those receiving multiple inoculations. Research is needed to determine which inoculants cause the highest blood histamine level, or histaminemia, and when it peaks.

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1. INTRODUCTION

Conventional teaching in pediatric pathology contends that subdural hemorrhage and retinal petechiae, without any history of major trauma, should be considered as indicative of child abuse. Diagnoses such as “shaken-baby syndrome” are often made, without any evidence that the infant was abused and without any consideration of intrinsic capillary or venular fragility.

We are indebted to Fung et al. [1] at the Prince of Wales Hospital in Hong Kong for having the insight and the integrity to question this conventional teaching. She and her colleagues found no history of shaking or physical abuse of the patient, or in the infant’s family, in any of nine cases of subdural hematoma reviewed. These authors suggest that the pathognomonic association between subdural hematoma/retinal hemorrhages and child abuse may be a “self-fulfilling prophecy.” It certainly seems to be a self-propagating assumption.

An erroneous diagnosis can have catastrophic consequences, not only for the infant but also for the infant’s family: a shaken-baby diagnosis involving infant death often leads to prosecution of one or other parent, or a babysitter, for killing the infant. It is tragic enough for one to lose a child, without being wrongly accused of murder and possibly sentenced to life in prison. The injustice of these prosecutions is reflected by the way the blame is usually assigned to the last person holding the infant when it stopped breathing, rather akin to the childhood game of “musical chairs.” As noted by Plunkett [2], “The last person standing when the music stops is the one who must have injured the child.”

The question addressed in Court is, “Who killed this infant?” — while the real question is, “What was the cause of this infant’s death?” The question of cause can sometimes be investigated while the child is still alive, by studies of skin capillary fragility, and by determinations of plasma ascorbic acid and whole blood histamine levels. Moreover, subdural hemorrhages can sometimes be detected by ultrasound examination before birth and even before labor [3,4]. Never assume that bruises and broken ribs, or other broken bones, must always indicate trauma, because variants of infantile scurvy (or Barlow’s disease) still occur today.

If not child abuse, what then could have been the cause of the very serious cerebral hemorrhages causing spastic quadriplegia in four infants, and lesions such as convergent squint, epilepsy, and delayed development in others studied by Fung?

2. CAPILLARY OR VENULAR FRAGILITY

A. VITAMIN C DEPLETION

No blood coagulation defect was found in any of the infants, so one has to consider capillary fragility as a possible cause. As an obstetrician, I am reminded that cerebral and retinal hemorrhages sometimes occur in women with excessive vomiting in pregnancy. Very severe cases of hyperemesis gravidarum in these women led to Wernicke’s hemorrhagic encephalopathy and death, until Lund and Kimble [5] of Madison, Wisconsin, in 1943, wrote:

“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.”

For some reason, vitamin C depletion occurs very rapidly in hyperemesis gravidarum. Whenever a woman complains of excessive vomiting in pregnancy and is found to have acetone or acetoacetic acid in her urine, due to starvation, even for a few days, she should be admitted to hospital and treated with intravenous dextrose, saline, and vitamins B complex and C.

In this context, we should also remember the important, indeed seminal, studies of Kalokerinos [6] working in Australia. In 1974, he reported that infant deaths following inoculations in aborigine children could be prevented by prior treatment with vitamin C. He should have received worldwide recognition for this pearl of clinical science, but his writing has yet to be fully appreciated by public health policymakers. Indeed, very few physicians provide vitamin C with inoculations even today. Undoubtedly, the aborigine infants were unduly sensitive to the usual vaccines administered in first-world countries, as their mothers had not yet been

exposed to our diseases and could not provide adequate maternal immunity in their milk.

Perhaps the current lack of physician interest in vitamin C is due to the belief that vitamin C deficiency does not occur in the modern world. It certainly does in adults, for the National Health and Nutrition Survey (NHANES III) [7] for the years 1988-94 revealed serum ascorbic acid deficiency (<0.2 mg/100 mL) in 12% of Caucasians, 15% of African-Americans, and 9% of Mexican-Americans. Moreover, Johnston and Thompson [8] reported the results of analysis of blood plasma samples from 494 men and women attending a Health Maintenance Organization (HMO) clinic in Arizona, during a ten-day period in 1998. They found normal plasma ascorbic acid levels (0.5-1.6 mg/100 mL, or 28.4-90.9 $\mu\text{mol/L}$) in 64 percent, depleted levels (0.2-0.5 mg/100 mL, or 11.4-28.4 $\mu\text{mol/L}$) in 30 percent, and deficient levels (<0.2 mg/100 mL, or <11.4 $\mu\text{mol/L}$) in 6 percent of the subjects.

The reason that many vitamin C-deficient patients remain undiagnosed and untreated, is that they can present in so many ways with so many different symptoms, such as backache due to incipient spinal disc disease. No one thinks of vitamin C deficiency unless the patient has severely bleeding gums, but bleeding gums are never seen in infants before the eruption of the teeth. Unfortunately, few if any hospitals, as yet, conduct plasma vitamin C analysis as a routine test.

Many pediatricians believe that vitamin C deficiency could not possibly occur today. Fresh breast milk from a healthy mother usually contains enough vitamin C, and the formula used for bottle-fed infants is also quite adequate when it is supplemented with the proper fruit juice. Today it is the fashion to give apple juice instead of orange juice as a nutritional supplement for bottle-fed infants, but apples are a poor substitute for oranges. One hundred grams of fresh orange juice (3-1/4 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 and can afford to buy apple juice fortified with additional vitamin C, there may still be a risk of vitamin C deficiency. Vitamin C loss may also occur when the milk in the feeding bottle is heated too much, as in a microwave oven.

B. HISTAMINEMIA

In 1980, when I was working in Brooklyn, New York, I had the privilege of reporting [9] a highly significant elevation of the blood histamine levels of ambulant men and women who had low plasma ascorbic acid levels. None of these people had been placed on an abnormal diet, but 34 percent of them had subnormal and 3 percent had markedly deficient ascorbate levels (<0.2 mg/100 mL, or <11.4 $\mu\text{mol/L}$). They were doctors, nurses, medical students, secretaries, and ambulant prenatal patients who volunteered to give blood. The ascorbate-depleted people were outwardly indistinguishable from the rest. As a matter of interest, the lowest plasma vitamin C level and the highest blood histamine level were found in one of our resident physicians after a night on duty.

A highly significant inverse logarithmic relationship was found between the plasma ascorbic acid and the blood histamine levels in the same samples (FIG. 1). The blood histamine level was increased four- to fivefold in the vitamin C-depleted subjects. Classical scurvy, with bleeding gums, does not occur until the blood histamine is increased more than tenfold. The reason for this large increase in the blood histamine level is that ascorbic acid is essential for the elimination of histamine by conversion to hydantoin-5-acetic acid and on to aspartic acid *in vivo*, as shown by Chatterjee et al. [10]. The blood histamine level rapidly returns to normal when ascorbic acid is provided by mouth.

Electron-microscopic studies of guinea pigs by Gore et al. [11] (FIG. 2) showed opening of the tight junctions between the endothelial cells of the small blood vessels in those with scurvy. Similarly, Majno and Palade [12] (FIG. 3) showed widening of the endothelial junction gaps and leakage of tracer particles through these gaps in rats, following the injection of histamine. It is evident that an elevated blood histamine is the most likely cause of the widespread capillary fragility and bleeding in vitamin C deficiency and scurvy.

There is a disturbance of proline and lysine metabolism in scurvy, and this is responsible for a defect in the formation of collagen fibers, which are the matrix for the foundation of fibrous tissue, bone, cartilage, dentin, and tooth cement. Some have suggested that it is this collagen defect which is

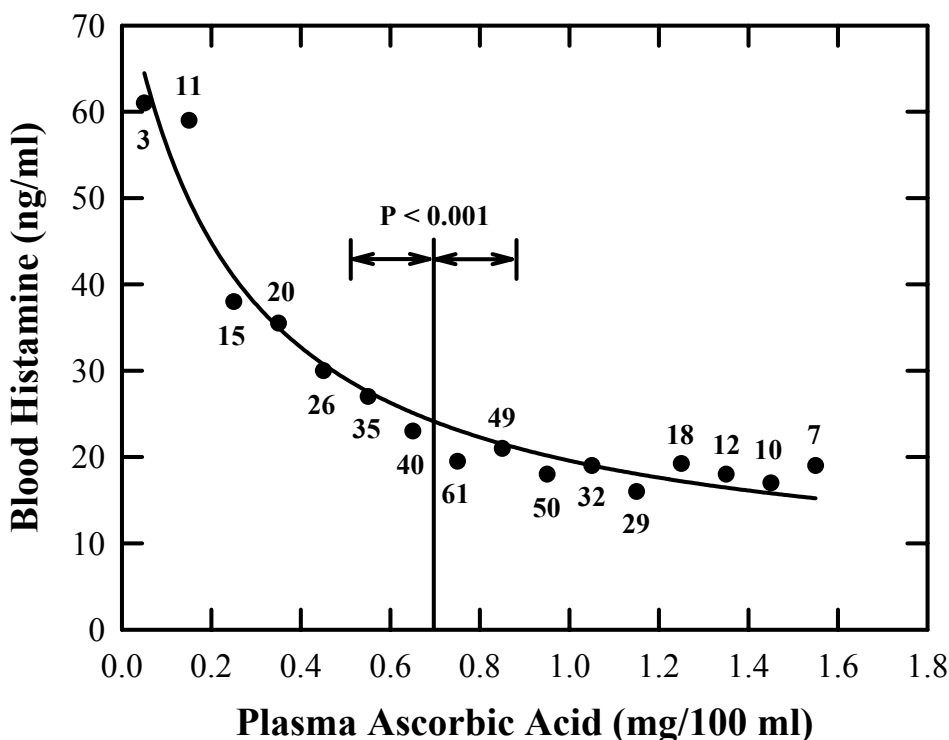


FIGURE 1. RESULTS OF PLASMA ASCORBIC ACID (REDUCED FORM) AND WHOLE BLOOD HISTAMINE CONCENTRATIONS IN THE SAME BLOOD SAMPLES FROM 437 HUMAN VOLUNTEERS IN BROOKLYN NY (1980). A highly significant increase in the blood histamine level was evident when the plasma ascorbic acid level fell below 0.7 mg/100 mL. This comprised 150, or 34 percent, of the 437 men and women. Constructed from data in TABLE 1 of Clemetson [9], and the number beside each data point denotes the sample size.

responsible for the bleeding in scurvy; however, there is very little fibrous tissue surrounding the capillaries and venules from which the bleeding stems.

Ascorbic acid is undoubtedly the most effective antihistamine. Other antihistamines used for the relief of maladies such as allergic rhinitis or excessive gastric acidity do not remove histamine from the blood. They act only by blocking H1 and H2 receptors, respectively.

C. INFECTION

Hume and Weyers [13], when studying ascorbic acid levels during the common cold, were fortunate enough to have obtained and analyzed blood samples from four out of seven volunteers during the week before the onset of the symptoms. They

found that the leukocyte ascorbic acid level fell from a normal value of 20.0 to a low level of 10.3 $\mu\text{g}/10^8$ white blood cells on the first day of symptoms. It is quite clear that a similar ascorbic acid depletion accounted for the post-vaccination deaths of so many aborigine infants treated by Kalokerinos. They nearly all had runny noses, and the deaths ceased in those who received vitamin C supplements.

Chorio-amnionitis, otitis media, and pneumonia are much more serious infections requiring vitamin C supplementation. These diseases would clearly call for postponement of any infant inoculations. Although infection causes the release of many toxic substances into the blood and tissues, the level of histamine in the blood is of the utmost importance. A reduction of the blood histamine concentration seems to be critical for survival, both in animals and



FIGURE 2. ELECTRON MICROGRAPH OF SCORBUTIC GUINEA-PIG AORTIC ENDOTHELIUM. Note the widened intercellular junction gaps. From Gore et al [11]. With permission from the American Medical Association.

in man. This can be achieved simply by vitamin C supplementation.

D. IMMUNIZATIONS

Studies on guinea pigs by Harde [14], by King and Menten [15], by Jungblut and Zwemer [16], and

by Kligler [17] have shown that deficiency of vitamin C increases the vulnerability of these animals to diphtheria toxin. King and Menten observed that there is a wide zone of vitamin C deficiency, without the appearance of scurvy, where physiological processes are subnormal and the animal is more sensitive to bacterial toxins.



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 [12]. With permission from the Rockefeller Institute Press.

A review of the literature on this subject [18] has shown that vitamin C also protects against four varieties of gas gangrene and against tetanus clostridia toxins. This was observed even in rats and mice, which synthesize their own ascorbic acid from simple sugars in the liver. Clearly, these animals do

not always make enough for all their needs. It would seem that ascorbic acid does not inactivate the individual toxins; it simply removes the histamine released by the effect of the toxins, or toxoids, in animal tissues.

The observation by Chatterjee et al. [10], that vaccines and toxoids cause a significant increase in the blood histamine levels of guinea pigs, opens up a wide area for discussion. We should not be surprised that the injection of foreign proteins leads to a release of histamine; the fact that this histaminemia can be modified or prevented with ascorbic acid is of profound significance.

3. DIFFERENTIAL DIAGNOSIS

Two pathologists, several other physicians, and many parents now question the tenets upon which the diagnosis of “shaken-baby syndrome” is made [19-22]. Many infants die with retinal petechiae and subdural hemorrhages, without any evidence of trauma. We need to understand their problem.

Barlow’s disease, or infantile scurvy, was well recognized in bottle-fed infants in the first half of the 20th Century and was usually associated with poverty and ignorance of the parents. Actually, Barlow’s disease also occurred in the infants of more prosperous families, due to the common practice of boiling cow milk to destroy all tuberculosis bacteria. It was the heat that destroyed the vitamin C.

Now it seems that we have a variant of Barlow’s disease — occurring in younger infants, and having fewer of the flagrant signs of full-blown scurvy such as extensive bruising, rib fractures, epiphyseal separations, and indolent ulcers. The diagnosis of infantile scurvy, or Barlow’s disease, has become rare, and the term “shaken-baby syndrome” seems to be replacing it in frequency. Moreover, this new Barlow’s Disease Variant seems to occur most often within two or three weeks after multiple vaccinations, or soon after an infection. We must realize that the histaminemia produced by injection of the foreign proteins, as toxins or toxoids, will compound the histaminemia of moderate ascorbic acid depletion, so as to cause a hemorrhagic fragility state.

Although a Barlow’s disease variant may be the most common disease, other diagnoses such as fragile bone disease, hemorrhagic disease of the newborn, and glutaric aciduria type 1 must also be considered.

4. CLINICAL SUGGESTIONS

1. Vaccinations should be postponed for any infant who is premature, has an upper respiratory infection, or is ailing in any way.

2. We should reexamine the policy of giving as many as six inoculants all at once to infants at eight weeks of age.

3. Every infant should receive 500 mg of vitamin C powder or crystals, in fruit juice, to drink before inoculations.

4. Any infant showing severe reactions to the immunizations, such as convulsions or a high-pitched cry, should receive additional ascorbic acid by injection.

5. Plasma vitamin C and blood histamine analyses should become a routine part of the work-up for all severely ill infants.

5. RESEARCH PROPOSAL

In years past, we all received one, two, or three inoculations in infancy; but now that infants receive as many as six inoculants together at eight weeks of age, we must evaluate the impact of injecting so many foreign proteins on the same occasion. Every antigen used for inoculation has been extensively tested before approval, but the effect of introducing all these antigens at once, may be quite another matter and may be too much of a challenge for a susceptible infant. We must consider not only the individual toxicities of these toxoids, but also the possibility that the toxicity of two inoculants given together may be more than twice that of one alone.

One way to evaluate this will be to study whole blood histamine and plasma ascorbic levels before and after single and multiple inoculations. This study will be best conducted in adults, as the question of consent from guardians can be a sensitive issue, and we do not want to remove too much blood from infants just for research purposes. It must be noted that 20 mL blood samples were used in our study of adults (FIG. 1) so as to obtain enough blood for duplicate analyses for each substance.

It has therefore been proposed [23] that a study be conducted on soldiers, sailors, airmen, and marines being posted overseas, both before and at

different intervals after single or multiple inoculations. It is anticipated that those with low plasma ascorbic acid levels will show the greatest rise in whole blood histamine. Moreover, we can expect that multiple inoculants will cause a greater histaminemia than a single inoculant. It will also be possible to find out which inoculant causes the greatest histaminemia, when it peaks, and how long this lasts.

Care must be taken to learn accurate plasma ascorbic acid (AA) and whole blood histamine analytic methods, and to study the effects of plasma storage at different temperatures. Any pink-colored blood plasma must be discarded, as hemolysis causes a rapid destruction of AA. Care must also be taken to dry AA crystals or powder over calcium chloride in a dessicator, as AA is hygroscopic. Any internal or external standards prepared by weighing moist ascorbic acid crystals will give falsely high plasma analyses, if this precaution is not taken.

6. ORIGINS OF THIS THESIS

It was the excellent work of Kalokerinos [6] which showed that AA was so valuable in preventing infant deaths following the usual inoculations. Chatterjee et al. [10] revealed an inverse relationship between plasma ascorbic acid and whole blood histamine levels in guinea pigs. My own work [9] revealed an exponential increase in the human blood histamine level, which was evident even in the 34 percent of normal, ambulant people who had subnormal but not actually deficient AA levels.

7. ANTICIPATED BENEFITS

The present article is designed to provide a full explanation of Kalokerinos' findings and to demonstrate the possibility of: (i) preventing many infant deaths, (ii) preventing many wrongful prosecutions and convictions of parents and caregivers for shaken-baby syndrome, and (iii) reducing the incidence of all the serious neurological consequences of cerebral hemorrhage due to capillary fragility in infants.

The simple and inexpensive practice of giving supplemental vitamin C may have markedly

beneficial effects on infant morbidity and mortality. This should not be surprising, for our inability to synthesize ascorbic acid is the human inborn error of metabolism shared by all of humanity.

8. THE FUTURE

We can look forward to the time when medical instrument manufacturers may be able to devise a simple intravenous or intramuscular needle method for the estimation of AA by virtue of its powerful redox potential. Alternatively, chemists may be able to devise a simple and rapid technique for measuring both AA and histamine in a small volume of blood.

Once the principle of compounded histaminemia has been established in connection with the military inoculations, the information gleaned can be extended to the question of infant immunizations.

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