

Vaccines, Apparent Life-Threatening Events, Barlow's Disease, and Questions about "Shaken Baby Syndrome"

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ABSTRACT

Apparent Life-Threatening Events (ALTEs), as defined by the National Institutes of Health, encompass all the findings hitherto attributed to "Shaken Baby Syndrome" (SBS), and may follow routine vaccination. Vaccines may also induce vitamin C deficiency (Barlow's disease), especially in formula-fed infants or infants whose mothers smoke. This could account for some of the changes seen in these infants, including hemorrhages, bruises, and fractures. Vitamin C deficiency should be excluded in patients suspected to have SBS.

Definitions

"Shaken baby syndrome" (SBS) is a collection of findings, not all of which may be present in any individual infant diagnosed to have the condition. Findings include intracranial hemorrhage, retinal hemorrhage, and fractures of the ribs and at the ends of the long bones. Impact trauma may produce additional injuries such as bruises, lacerations, or other fractures.¹

The National Institutes of Health, at its 1986 Health Consensus Development Conference on Infantile Apnea and Home Monitoring, defined "Apparent Life-Threatening Event" (ALTE) as an episode that is frightening to the observer and is characterized by some combination of apnea (central or occasionally obstructive), color change (usually cyanotic or pallid but occasionally erythematous or plethoric), marked change in muscle tone (usually marked limpness), and choking or gagging. In some cases, the observer fears that the infant has died. ALTE is not so much a specific diagnosis as a description of an event.

Overview

SBS is often suspected in infants who present with unexplained bruising, subdural hemorrhages, and retinal hemorrhages. Manual shaking with whiplash-induced intracranial and intraocular bleeds is thought to be the most likely cause of these injuries.²⁻⁶ However, on questioning, most parents and caregivers vehemently deny having shaken or harmed the baby. Could the symptoms classically attributed to SBS actually have another cause?

In the case reports that follow, further analysis of the clinical, laboratory, and postmortem features in infants diagnosed with SBS suggests the possibility of an alternate explanation for their subdural hemorrhages, retinal hemorrhages, and bony lesions or bruises. In each of these instances, an ALTE occurred. All the caregivers involved in these cases have strongly and repeatedly rejected the notion of nonaccidental injury or SBS.

Geddes et al.⁶ have hypothesized that in the immature brain, hypoxia alone is sufficient to activate the pathophysiologic cascade that culminates in dural hemorrhage. Is it possible that ALTE, when associated with anoxia and cyanosis, could cause subdural hemorrhage in conformity with the Geddes hypothesis?

Moreover, the clinical picture of Barlow's disease, infantile vitamin C deficiency, resembles that of "battered baby"⁷ or child abuse,⁸ as it may also present with multiple hemorrhages and fractures.

Case 1

A male infant was born to a 20-year-old mother after a 41-week gestation by normal vaginal delivery. His Apgar scores were 8 at one minute and 9 at five minutes. Injections of vitamin K 1 mg (IM) and hepatitis B vaccine (Hep B) were given. During pregnancy the mother had a urinary tract infection and iron-deficiency anemia and had been treated with an antibiotic and ferrous sulfate. The infant was breastfed for two months and then fed formula. The mother smoked about 10 cigarettes per day.

At the infant's routine check at age 2 months, his navel had still not healed, and some bright red discharge was noted. Immunizations consisting of diphtheria, tetanus, and acellular pertussis (DTaP), *Hemophilus influenzae* B (Hib), and Hep B vaccines were given. These were repeated two months later.

On the night after the second set of immunizations, the mother said the infant was "fussy," and she gave him Tylenol. The following day the baby's father gave him a bath and put him on the bed while he attended to some other matter for about two minutes. When he returned, he found that the infant was limp, unresponsive, and not breathing. Shortly thereafter the infant became blue.

On arrival at the nearest hospital, the infant was found to be pulseless. He was intubated and mechanically ventilated, and his pulse was restored. Examination revealed evidence of an intracranial bleed and bilateral retinal hemorrhages. The magnetic resonance imaging (MRI) report stated: "There is abnormal restricted diffusion and decreased apparent diffusion coefficient in the entire territory of the bilateral anterior and posterior cerebral arteries and partial left greater than the right middle cerebral arteries. These findings are consistent with acute ischemic infarction. Minimal extra-axial parafalcine interhemispheric hyperintense signal on T1 and diffusion weighted images is likely a small [acute] subdural hemorrhage. Effacement of the sulci in the areas of infarction is consistent with edema. No evidence to suggest posterior fossa infarct is demonstrated."

In addition, another report noted "subdural hemorrhages [presumed to be acute] extending from the posterior fossa, through the foramen magnum, and along the dorsal cord to the inferior endplate of C3. No cord compression or deformity."

Multiple computerized axial tomographic (CAT) sections of the head were obtained without contrast and showed “findings consistent with sub-arachnoid hemorrhage as well as cerebral edema associated with anoxia.”

A skeletal survey showed “findings consistent with a nondisplaced fracture of the distal left tibia,” and two weeks later the report stated, “the previously noted nondisplaced left distal tibial fracture is not well seen.” The possibility of temporary brittle bone disease as described by Paterson et al., who attributed it to a temporary deficiency of an enzyme in the post-transitional processing of collagen,⁹ was apparently not considered.

Blood studies showed a prothrombin time of 17.9 sec (normal range, 8.2–14.1); partial thromboplastin time, 35.5 sec (28.0–50.0); aspartate aminotransferase, 97 U/L (20–60); glycine, 131 $\mu\text{mol/L}$ (224–514); lysine, 66 $\mu\text{mol/L}$ (114–269); hemoglobin, 11.0 g/dL (10–13.5); platelets, $382 \times 10^9/\text{L}$ (150–450); pH, 7.26 (7.35–7.45); bicarbonate, 18.2 mmol/L (21–29); and glucose, 188 mg/dL (60–80).

The recorded diagnoses were “non-accidental injury” and “shaken baby syndrome.” The infant survived, but was developmentally delayed and required a gastrostomy.

Case 2

A female infant was born at term weighing 2.9 kg. The mother had almost daily vomiting throughout the pregnancy and weighed less after delivery than she did before she became pregnant. Because of the persistent vomiting, she was unable to consume the vitamin and iron supplements she was advised to take. She also smoked during her pregnancy. The infant was given an IM injection of 1 mg vitamin K at birth. She was formula fed.

At about three weeks of age the infant suddenly awakened from her sleep, screaming. The mother interpreted the scream as a cry of pain rather than hunger. The infant vomited, and then settled after a short interval.

While bathing the infant the next morning, the mother noticed a deep purple bruise on her arm. Another bruise appeared about 2 cm from the first one. No investigations were done to establish the cause of these bruises.

Following this episode the infant was reasonably well, and at age 7 weeks weighed 4.25 kg. She was given DTaP, Hib, and meningitis C vaccines at 8 weeks. From then on, she refused her regular feedings and started vomiting, and was therefore admitted to the hospital six days after the vaccinations.

After discharge from hospital, while being bottle-fed by the father 11 days after being vaccinated, she “suddenly collapsed, stopped breathing, and went floppy.” The physician on emergency call found the baby “very blue initially” and said she may have been “hypoxic for 6–8 minutes.” CPR was attempted and the infant was admitted to the hospital, where she was intubated and resuscitated, but died shortly afterward.

Radiological findings included a subdural hemorrhage, 12 “fractures” involving all four limbs, and seven rib “fractures” of varying ages. These findings were confirmed at post-mortem examination.

Radiologic and postmortem examinations showed that the anterior ends of the third through tenth ribs were “broadened” bilaterally. This is consistent with the typical “scorbutic rosary” alluded to in Nelson’s *Textbook of Pediatrics* in which, referring to infantile scurvy, it is stated: “A ‘rosary’ at the costochondral junctions and depression of the sternum are other typical features.”¹⁰

Other relevant laboratory results were as follows: Factor VIII, 221 IU/dL (normal range 50–125); von Willebrand factor antigen, 253 IU/dL (50–246); fibrinogen, 4.0 g/L (1.7–4.0); alkaline phosphatase, 321 U/L (65–265); alanine transaminase, 59 U/L (5–45); lactate, 6.6 mmol/L (1.1–2.2); calcium, 2.32 mmol/L (2.37–2.74); albumin, 28 g/L (35–55); lysine, 55 $\mu\text{mol/L}$ (100–300); hemoglobin, 9.0 g/L (10–13.5); lymphocytes, $2.80 \times 10^9/\text{L}$ (3–13.5); and eosinophils, $0.01 \times 10^9/\text{L}$ (0.1–0.3). In addition to lysine, the levels of six other essential amino acids were reduced. Levels of glutamine and two other nonessential amino acids were also reduced.

Autopsy revealed subdural and subarachnoid hemorrhages, cerebral edema, and widespread acute ischemic changes.

There was general agreement among the pediatricians, radiologists, and pathologists that the varying age of the lesions indicated repeated episodes of violent abuse such as shaking, and that death was caused by nonaccidental injury. Yet there had been no evidence of injury or other reason to suspect abuse at the time of hospitalization, or in the many visits to the doctor’s office. The origin of the “fractures” remains undetermined; however, given the compromised nutritional status of the baby in utero, fractures could be caused by temporary brittle bone disease.

Discussion

The current concept of SBS includes intracranial bleeding, usually in the form of a subdural hematoma, which may be acute or chronic; parenchymal injury and/or anoxic changes in the brain; skull fracture (if impact occurred); and retinal hemorrhages. Constant features are subdural and retinal hemorrhages. Various fractures including those of the long bones and ribs are often used to support an impression of child abuse, but it should not be forgotten that Barlow’s disease can resemble “battered baby.”⁷

As far as we are aware, no one has measured the blood levels of vitamin C or histamine in cases of suspected SBS. The possible existence of vitamin C deficiency is therefore hypothesized from clinical, radiological, and other laboratory findings. There are several features, common to both cases, that predispose to or are consistent with a diagnosis of vitamin C deficiency:

1. The mothers had documented nutritional problems and were unwell during their pregnancies.
2. The mothers smoked during their pregnancies, thereby lowering their own and their infants’ vitamin C levels.
3. Both infants were being formula fed at the time of their illnesses, and the mothers were not advised to give supplemental vitamin C.
4. Both parents reported early evidence consistent with Barlow’s disease: spontaneous bruising in one infant and delayed wound healing in the other.

5. Both infants had deficiencies in essential and nonessential amino acids necessary for the production of normal collagen, which is essential to prevent scurvy.

6. Both infants had evidence of liver dysfunction.

7. Unexplained “fractures” were recorded in both children.

In addition to the low amino acid levels, the second infant had additional evidence of malnutrition in that the serum albumin, calcium, and hemoglobin levels were all low.

Animal experiments have demonstrated that administration of vitamin C can counter some of the ill effects of nicotine in newborns.¹¹ This suggests that mothers who smoke may compromise vitamin C levels in their children.

One essential function of vitamin C is maintenance of normal connective tissue by the hydroxylation of proline and lysine in procollagen, using the enzyme prolyl hydroxylase with vitamin C as a cofactor.¹² While vitamin C has numerous other functions, this one maintains the integrity of the blood vessels, bones, and dentine, which is compromised in scurvy, leading to the manifestations that might be mistaken for SBS. A lack of normal collagen causes capillary walls to break down, and hemorrhaging may occur from any site in the body. Expansion at the ends of the costochondral junctions is highly suspicious for scurvy, and should in itself have raised questions about the diagnosis of SBS.

Formula feedings are often heated before being given to the infant, and heat destroys vitamin C. Under such circumstances, vitamin C supplements are needed to prevent scurvy. Neither infant received a supplement.

The increased level of von Willebrand factor antigen in the second infant could be the result of the release of the antigen from scurvy-disrupted capillary endothelial cells in which it is produced. Alternatively, von Willebrand factor is a known acute phase reactant that is possibly increased in response to the stimulus of vaccination.

Clemetson has shown that increasing levels of blood histamine are accompanied by lower vitamin C levels.¹³ As part of the immune response to vaccines, mast cells liberate histamine, causing further widening of the intercellular spaces between the vascular endothelial cells in children who may have subclinical scurvy. Although it has not been established that vaccinations cause vitamin C deficiency, the inverse relationship between histamine and vitamin C levels in the blood would support the hypothesis that vaccinations could lead to vitamin C deficiency, and might explain spontaneous bleeding.

Follis, reporting the sudden deaths of three infants with scurvy, observed that “the liver was yellowish” and “showed atrophy of the central cells and a good deal of fatty infiltration.”¹⁴ As noted, some liver enzymes in both infants were abnormal.

Post-immunization deaths in aboriginal children in Australia were greatly reduced when Kalokerinos administered vitamin C by IM injection before, and sometimes after, immunizing the child.¹⁵ Many of these children had the classical signs and symptoms of scurvy.

Conclusion

Although neither vitamin C levels nor histamine in the blood were measured, clinical, radiological, and laboratory findings suggest that the diagnosis of SBS should be questioned in these two

cases. Poor nutrition and possible vaccine-induced vitamin C deficiency associated with temporary brittle bone disease may represent alternative explanations. Infantile scurvy, while uncommon in affluent countries, should nevertheless be routinely excluded before a diagnosis of SBS is made.

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