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CT Diagnosis of Toxic Brain Injury in Cyanide Poisoning: Considerations for Forensic Medicine

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Two deaths occurred after ingestion of cyanide-containing Extra-Strength Excedrin capsules. Cranial CT scans obtained within 3 hr of each patient's collapse showed diffuse cerebral swelling and loss of gray-white differentiation. Most diffuse cerebral insults (hypoxia, ischemia) do not show such changes so soon after injury. The early onset of diffuse cerebral edema with loss of gray-white differentiation may be a clue to the diagnosis of acute cyanide poisoning.

Cyanide is one of the most rapidly acting poisons; symptoms can occur within seconds of hydrogen cyanide gas inhalation and within minutes of skin contamination by or ingestion of cyanide salts. Cases of genocide, homicide, suicide, and accidents relating to cyanide-containing substances are well known. Hydrocyanic (or prussic) acid and its derivatives are used for fumigation of ships and warehouses and as fertilizer (cyanamide). Cyanide salts are used in electroplating, metallurgy, metal cleaning, hide dehairing, and organic synthesis, and are found in photographic chemicals and rodenticides. Cyanogenic glycosides, such as amygdalin, release cyanide on enzymatic breakdown, and are components of the leaves, bark, and seeds of many plants, including peach, apricot, plum, chokecherry, cassava, and bitter almond. Laetrile, a synthetic amygdalin, has been used for cancer therapy and has also caused poisonings [1–5].

Acute cyanide poisoning may be difficult to diagnose, and may masquerade as a natural death, with nonspecific clinical and autopsy findings. We describe two deaths that were initially considered "natural" and that later findings revealed to be due to acute cyanide poisoning resulting from the ingestion of cyanide-adulterated Extra-Strength Excedrin capsules. Cranial CT scans performed within 3 hr of collapse showed rapidly developing diffuse cerebral edema with poor demarcation of the gray-white junction. This finding may be a clue to the diagnosis of acute cyanide poisoning.

Subjects and Methods

Patients were imaged on a GE CT/T 9800 scanner using contiguous axial 10-mm slices from the base of the skull to the vertex without IV contrast. Whole blood and serum cyanide concentrations were determined by colorimetric and potentiometric methods, the latter utilizing a cyanide-specific electrode [6].

Case Reports

Case 1

A 40-year-old previously healthy woman was found unresponsive, having been seen alive 10 min earlier. Paramedics described her as comatose and hypotensive. Cranial CT performed 1¾ hr after collapse showed diffuse cerebral edema with marked effacement of sulci and brainstem cisterns (Fig. 1). The gray-white differentiation was poorly seen. Death occurred

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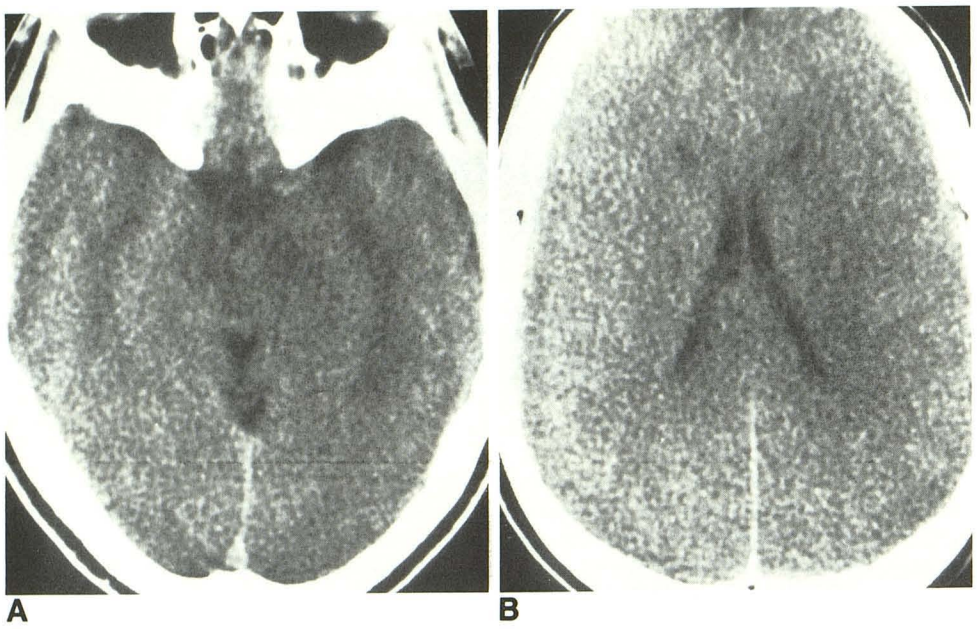

Fig. 1.—Case 1. Noncontrast CT scans.
***A*, Level of midbrain. Effacement of quadrigeminal plate cistern and other basal cisterns.**
***B*, Level of lateral ventricles. Compression of ventricles and sulci with loss of gray-white differentiation.**

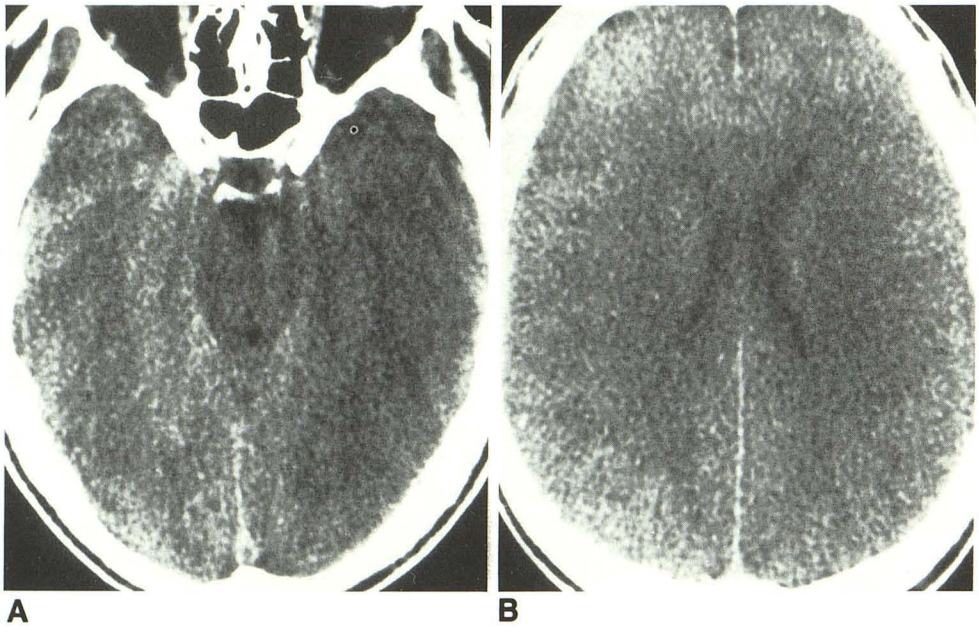

Fig. 2.—Case 2. Noncontrast CT scans.
***A*, Effacement of basal cisterns.**
***B*, Compression of lateral ventricles and sulci with loss of gray-white differentiation.**

5½ hr after collapse and was initially considered to be from natural causes.

The autopsy was remarkable for mild diffuse cerebral edema. No gastritis was observed. A transient and faint odor suggesting cyanide was detected by one observer. An autopsy blood cyanide level (20 hr after death) was 2.4 mg/l. Cyanide concentrations performed on samples obtained 2 hr after collapse were 4 mg/l in blood and 0.5 mg/l in serum. Additional testing by the U.S. Food and Drug Administration (FDA) identified cyanide in some of the capsules in a bottle of Extra-Strength Excedrin* found in the deceased's home. Further investigation indicated that product tampering was the likely source of the cyanide-containing capsules. The death was attributed to acute cyanide poisoning and was classified as homicide.

Case 2

A 52-year-old previously healthy man collapsed in the presence of his wife. In the emergency room, he was comatose with refractory hypotension and metabolic acidosis. He died about 4 hr after collapse. A cranial CT scan performed 2½ hr after collapse showed marked diffuse cerebral edema with compression of sulci and brainstem cisterns and diffuse loss of the gray-white differentiation (Fig. 2). Clinically, the death was thought to be from natural causes.

* Bristol-Meyers, New York.

A nonforensic hospital autopsy 12 hr after death attributed death to severe pulmonary emphysema. The only other finding was diffuse cerebral edema.

After the death described in case 1 and subsequent media attention, the widow of the second patient inspected her home and found two bottles of Extra-Strength Excedrin capsules. These were analyzed by the FDA and found to contain cyanide-adulterated capsules. The patient was known to have ingested capsules minutes before collapse. Testing performed 12 days after the autopsy on serum obtained at autopsy showed a serum cyanide concentration of 0.5 mg/l. Cyanide could not be detected in either case in formalin-fixed tissue by colorimetric or potentiometric methods. The second death was recertified as due to acute cyanide poisoning and was reclassified as homicide.

Discussion

The histotoxic effects of the cyanide ion are due primarily to its high affinity for iron in the ferric state. When absorbed, it reacts readily with the trivalent iron of cytochrome oxidase in mitochondria, thus inhibiting cellular respiration with subsequent cytotoxic hypoxia [7]. The fatal oral dose of hydrogen cyanide is estimated at 50–100 mg [8], but death has been reported from as little as 0.13 mg [9].

Cyanide poisoning may masquerade as natural disease, and can be difficult to diagnose both clinically and pathologically. The clinical signs are nonspecific and reflect cellular hypoxia, including altered consciousness progressing to coma; tachypnea progressing to respiratory depression and arrest; convulsions; and cardiac arrhythmias and hypotension. Laboratory abnormalities include an anion gap metabolic acidosis and the presence of bright red blood with a normal hemoglobin oxygen saturation. Although the bitter almond odor is characteristic, this may not be detectable when low concentrations of cyanide are present. In addition, 20–40% of persons are genetically unable to detect the odor of cyanide, and this ability cannot be learned [1].

The autopsy findings are similarly nonspecific; they include pulmonary and cerebral edema and, in cases of oral cyanide ingestion, erosive gastritis. However, in the two cases reported here, gastritis was not observed, probably because of both the small amount of cyanide ingested and the form of the ingested poison (contained in a gelatin capsule). Detection of the characteristic odor is diagnostic, but is subject to the same problems as in the clinical setting. Definitive diagnosis requires laboratory testing for cyanide, preferably in whole blood, although other body tissues and fluids may be used. If the diagnosis is not suspected, or the characteristic odor is not detected, the death might erroneously be attributed to natural causes [8].

Neuropathologists have been particularly interested in cyanide poisoning because of its strong tendency to damage white matter selectively. Gray-matter involvement is usually less and has been partially attributed to concomitant ischemic anoxia [10]. The most consistent white-matter change is demyelination, which has been described by several authors utilizing various experimental animal models [11–14]. However, Hirano et al. [15] showed the earliest changes in rat brains after cyanide poisoning to be swelling, vacuolation, and lysis of cell processes, particularly axons. The axonal swelling was accompanied by irregular empty zones, amorphous debris, occasional dilated vesicles, and swollen mitochondria, all well established within 1–2 hr. These changes were not considered secondary to generalized or local brain swelling, which occurs later, but rather to direct histotoxic anoxia.

The CT findings of marked diffuse cerebral swelling with associated loss of gray-white differentiation was seen in both of our cases and is also seen in more common situations, such as cardiac arrest and asphyxiation. However, the extremely rapid development of these radiographic findings (1¾ hr and 2½ hr) in our cases is characteristic of and nearly unique to cyanide poisoning. With global CNS hypoperfusion (e.g., cardiac arrest) Kjos et al. [16] observed diffuse mass effect, which was "often subtle," and loss of gray-white differentiation within 4 hr of the insult. However, these findings were absent at 2½ hr. In acute brain infarction, swelling is not radiographically detectable before 3 hr [17, 18], and it is subtle during the first 24 hr, reaching a maximum at 2–4 days [17]. Other causes of rapid development of cerebral edema include Reye's syndrome [19], head trauma [20], the "shaken infant syndrome" [21], water intoxication [22], and triethyl tin poisoning [23]. With Reye's syndrome the gray-white differentiation is increased [19]. CT scans after head trauma frequently demonstrate associated contusions, infarction, and subarachnoid hemorrhage. The "shaken infant syndrome" may only present with diffuse cerebral edema without external signs of child abuse, making the diagnosis difficult [21]. Water intoxication as a cause for cerebral edema is very rare and there is an associated profound hyponatremia [22]. Triethyl tin poisoning is also rare.

After cyanide poisoning, appropriate antidotal therapy and supportive measures may be lifesaving if initiated rapidly. Survival has been reported after ingestion of up to 6 g of potassium cyanide [3]. Unfortunately, neither laboratory testing nor CT scanning can be performed quickly enough to make them useful as determinants of whether to initiate therapy. However, even in the patient who is beyond therapeutic benefit, the CT abnormalities described may help establish the diagnosis, and in cases of homicidal "tampering" type poisonings, may prevent other deaths.

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