abstract

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Dr Lavezzi performed the histopathological examination, planned the study, analyzed all the findings in collaborative discussion with Dr Matturri, and wrote the manuscript; Drs Cappiello and Termopoli designed and performed the chemical characterization of pesticides in the brain sample; Dr Bonoldi carried out the autopsy and the clinical-anamnestic study; and all authors approved the final manuscript as submitted.

Ethical approval was granted by the Italian Health Ministry in accordance with Italian law 31/2006. Parents of the infant provided informed consent for both anatomicopathologic and toxicologic analyses, under protocols approved by the “Lino Rossi” Research Center Institutional Review Board of Milan University.

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Several of these sections, treated with the TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) immunohistochemical procedure to identify apoptotic cells, revealed the presence of positive neurons along the free border of this region.

Figure 1 shows the injured AP compared with that in an age-matched control subject who died of congenital heart disease. This alteration was not interpreted as being due to delayed development (ie, hypoplasia or agenesis) because the medullary surface in this area appeared ripped and eroded, with diffuse apoptotic neurons and deprived of the usual thin layer of flattened ependymal cells, all findings suggestive of the direct action of a harmful agent. No other alteration of the central nervous system was observed.

As required by the protocol of the “Lino Rossi” Research Center, a fresh sample of cerebral cortex, before brain fixation, was sent to the Liquid Chromatography-Mass Spectometry (LC-MS) Laboratory of the University of Urbino (Italy) for toxicologic investigation of environmental risk factors (eg, cigarette smoke, drugs, alcohol, air pollution, pesticides), which was performed according to the method proposed by Cappiello et al. Examination of the total ion chromatogram, in full-scan mode to search for nontargeted compounds with a mass ranging from 50 to 550 u., revealed in this case several matrix peaks. Most of them were fatty acids and endogenous matrix components, but one of the peaks with a strong mass range was related to the presence of 2,6-ditert-butyl-4-nitrophenol (DBNP) (Fig 2). This is a toxic contaminant, detected for the first time in a US navy submarine and identified by comparison with the reference spectra reported in the National Institute of Standards and Technologies electronic library (http://webbook.nist.gov/chemistry/), and has acaricide properties. According to the reports by her parents, which were collected according to routine investigative procedure in cases of sudden infant death by the medical staff, the infant was healthy until the day she suddenly and unexpectedly died.

However, our remarkable findings made it necessary to inquire more closely into the circumstances in which the death occurred. In particular, the presence of intense signal corresponding to DBNP on the toxicology screen prompted us to inquire further about exposures to environmental contaminants around the time of death. From this more in-depth investigation, we learned some additional information from the doctor who had examined the infant at death. The doctor reported that the father during the last 2 weeks of life had sprayed large doses of insecticide around the infant because of flies in the house. This information had not previously been reported to forensic investigators and helped explain the high levels of this toxin found during the toxicology screen.

**DISCUSSION**

We report here an unusual alteration of the AP that was discovered at histologic examination of the brainstem in a 7-month-old infant who suddenly died during sleep; the death was initially diagnosed as SIDS. SIDS represents the leading cause of postneonatal death in the developed world and is defined as the sudden, unexpected death of an infant <1 year of age that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history. The onset of the fatal episode mostly occurs during sleep, leading to the assumption that a subset of infants with SIDS have a dysfunctional maturation of neuronal centers involved in breathing control.

In this case we observed a ripped and eroded surface at the level of the AP, an alteration that we have never previously seen in our large series of SIDS neuropathology investigations (available at: http://users.unimi.it/centrolinorossi/en/publications.html), even in a specific study focused on this structure. The AP is a medullary formation devoid of the blood-brain barrier and, as such, enables blood-borne substances to arrive directly in the brain. However, the AP neurons function as chemosensors, preventing the transit of harmful agents. For many years, the AP has been...
considered a chemoreceptor trigger zone that can induce emetic reflexes in the presence of noxious chemical stimulations.\textsuperscript{11,12} Subsequently, experimental studies have disclosed additional important roles for this structure. In particular, it has been demonstrated that AP neurons receive peripheral vagal and baroreceptor afferent projections from the sensory neurons of the stomach, intestines, liver, kidneys, heart, and other internal organs.\textsuperscript{13,14} The AP neurons are able to send the collected information to important brainstem centers, such as the solitary tract nucleus, the dorsal motor vagal nucleus, and the dorsolateral pontine nuclei, assigned to the control of cardiovascular and respiratory functions.\textsuperscript{15,16} Therefore, the AP is ideally situated as a fundamental center of communication between visceral functions and neuronal control of vital activities.\textsuperscript{17} Consequently, lesions of the AP eliminate the brain’s modulatory role of the systemic autonomic state.

The erosion of the AP found in the present case resulted in the failure to identify toxic substances and to prevent their direct access to brainstem centers playing a vital role in the autonomic central control. The presence of this medullary alteration alone is sufficient to justify the infant’s death, thereby excluding the initial SIDS diagnosis.

In addition, the identification in the cerebral cortex sample of the infant of DBNP, an acaricide classified among "Hazard 6.1 (b)—Substances that are acutely toxic–fatal",\textsuperscript{18} aroused particular interest considering the high concentration. This finding indicates that the infant had absorbed substantial amounts of this toxic substance before death. Further investigations were then performed on the infant’s conditions of life before the death. Basic information had been revealed by the parents as soon as the event occurred at home (ie, the heavy, repeated use of insecticides around the infant). However, this specific circumstance was not mentioned either by the mother or father at the later interview. Furthermore, it is well known that retrospective information collected from the parents about possible risk factors after a fatal event are unreliable, probably due to an unconscious feeling of guilt.\textsuperscript{19}

In conclusion, the case presented here cannot be diagnosed as SIDS, because the peculiar alteration of the AP found in the brainstem was very likely caused by massive absorption of an insecticide. We believe this report to be important because it reveals that only an in-depth histopathologic examination of the brainstem, associated with an accurate, timely survey of the history and the circumstances in which the death occurred, can enable a correct differential diagnosis to be made in a case of sudden infant death and discriminate between a death due to a well-identified cause and SIDS. We underscore the importance of a careful appraisal of the death scene investigation, which should include interviews of witnesses and documentation about the residential environment. Every reasonable effort should be made in particular to identify possible exposure of the infant before death to harmful agents and chemical hazards. Furthermore, the medical staff must document the initial factual information obtained from parents and caregivers during the first minutes after their arrival on the death scene.

A limitation of this study is its focus on only a single case, so it does not allow generalization of the results to the wider population of a direct correlation between excessive use of household insecticides and brain damage. However, our report provides insight for further research in this direction. This case report represents a dire warning to the general public of the risks of indiscriminate use of toxic chemical contaminants. In particular, pediatricians and others providing health care to infants are reminded about the importance of counseling parents and other caregivers about the hazards of household chemicals and the importance of reading warning labels.

**ABBREVIATIONS**

AP: area postrema
DBNP: 2,6-ditert-butyl-4-nitrophenol
SIDS: sudden infant death syndrome
REFERENCES

Sudden Infant Death With Area Postrema Lesion Likely Due to Wrong Use of Insecticide
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