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## Sudden Infant Death Syndrome Is Serotonin the Key Factor?

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**N**EUROPATHOLOGICAL STUDIES HAVE IDENTIFIED A KEY role for the serotonin (5-hydroxytryptamine [5-HT]) pathways in sudden infant death syndrome (SIDS). Panigrahy et al<sup>1</sup> reported a decrease in 5-HT receptor binding in the arcuate nucleus, raphé obscurus, and other medullary regions that contain 5-HT cell bodies in SIDS cases in the United States. Similarly, Ozawa and Okado<sup>2</sup> reported a decrease in 5-HT receptor binding in the dorsal nucleus of the vagus, solitary nucleus, and ventrolateral medulla in SIDS cases in Japan. Subsequently, Kinney et al<sup>3</sup> confirmed their prior observations of altered 5-HT receptor binding in medullary regions in Native American Indians, a group at high risk for SIDS.

In this issue of *JAMA*, Paterson and colleagues<sup>4</sup> report that “SIDS cases had a significantly higher number and density of 5-HT neurons . . . and a significantly lower density of 5-HT<sub>1A</sub> receptor binding sites . . . in regions of the medulla involved in homeostatic function compared with controls” and that “the density of [5-HT transporter] binding relative to the number of 5-HT neurons in the medulla was significantly lower in SIDS cases compared with controls.” Further, Paterson et al<sup>4</sup> demonstrate that male infants who succumbed to SIDS had lower 5-HT<sub>1A</sub> receptor binding density in the raphé obscurus compared with female infants. Taken together, the evidence strongly supports extensive abnormalities in the 5-HT neuropathology of the medulla

in SIDS cases and begins to address the sex disparity in SIDS incidence. Recognizing that 5-HT influences a broad range of physiological systems including the regulation of breathing, the cardiovascular system, temperature, and the sleep-wake cycle, the study by Paterson et al<sup>4</sup> extends the available literature in support of the underlying hypothesis that SIDS is the result of 5-HT-mediated dysregulation of the autonomic nervous system.

While the published neuropathological data are derived from elegant studies, African American infants are one key group consistently underrepresented. Despite decreases in the SIDS incidence in the United States with aggressive Back to Sleep educational programs,<sup>5</sup> the final 2003 National Vital Statistics indicate a SIDS rate of 0.424 per 1000 live births for white infants but a rate of 1.152 per 1000 live births for African American infants.<sup>6</sup> These data reflect a 2.7-fold higher incidence among African American infants compared with white infants. Although this limitation of existing studies should not detract from the importance of the results, and the study describing Native American infants<sup>3</sup> does represent an at-risk study population, it suggests a need for expansion of the populations for future neuropathological studies from the primarily white and Hispanic infants recruited from San Diego<sup>1,4</sup> to those who more specifically represent the ethnicities of those who succumb to SIDS nationally.

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See also p 2124.

One solution is for medical examiners in regions with more representative ethnicity for SIDS to join forces in providing autopsy specimens for neuropathological researchers. An alternative solution is to encourage development of young neuropathological investigators (particularly in universities serving ethnically diverse populations, including African Americans) to pursue the study of SIDS in their own laboratories. In so doing, the next generation of neuropathological scientists studying SIDS will be secured, and infants more representative of the SIDS population can be included in research studies.

Another key concern is the limited sample sizes for SIDS cases and controls in the published neuropathological studies. The opportunity to perform these important studies is dependent on access to the neuropathological tissue. That access has been made possible, in part, under a California law<sup>7</sup> that renders it unnecessary to obtain informed consent from individual parents if tissue samples from their child are to be used for research on sudden and unexpected infant death. This statute was visionary and has allowed for remarkable progress in understanding the neuropathology of SIDS. If it were possible for more states to follow the lead of California, sample size and ethnic diversity for these essential SIDS studies would be expanded, controls could be matched in a 1:1 ratio with SIDS cases, and the desperately sought answers as to why SIDS continues to occur might be elucidated at a faster pace.

Currently, controls used in the neuropathological studies have typically died from a preceding illness or disease. Because of the possibility that current controls had an underlying susceptibility that increased their vulnerability to that illness, to death, or both, or that sequelae from the illness might affect their neuropathological findings, it seems possible that the reported controls may not reflect the "normal" condition. By broadening geographic sources, more controls who died from trauma or other unintended events without antecedent illness may be included.

As Paterson et al<sup>4</sup> clearly explain, data on infants in their study were collected after the successful implementation of the Back to Sleep message recommending that infants younger than 1 year should be placed on their backs to sleep, that they should be sleeping on firm surfaces, and that soft

bedding materials, overheating, and exposure to prenatal and postnatal cigarette smoke should be avoided. Despite remarkable progress made nationally in compliance with these known modifiable risk factors for SIDS, it is discouraging that 65% of the infants who succumbed to SIDS in the study by Paterson et al were in the prone or side sleeping position at the time of death. These results emphasize the critical need for reintroduction of the Back to Sleep campaign to educate parents and caretakers of young infants. Alternatively, it may be time to introduce more innovative interventions that focus on the different ethnic groups affected by SIDS.

While the neuropathological studies in SIDS are providing remarkable insight into the underlying mechanisms in the 5-HT pathways, identification of the definitive cause for SIDS will necessitate an expanded network of scientists and families working together toward the shared goal. They can join forces to influence legislation in their own states to replicate the success of the California program. Likewise, clinicians and researchers can gently inform parents who have lost an infant to SIDS about autopsy and the opportunity for their lost infant to contribute to the further understanding of SIDS. With 2162 infants dying from SIDS in the United States in 2003,<sup>6</sup> there is no time to lose in determining if serotonin is the key factor in the pathophysiology of SIDS.

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