

Multiple Serotonergic Brainstem Abnormalities in Sudden Infant Death Syndrome

David S. Paterson, PhD; Felicia L. Trachtenberg, PhD; Eric G. Thompson, MS; Richard A. Belliveau, BA; Alan H. Beggs, PhD; Ryan Darnall, BA; Amy E. Chadwick, BA; Henry F. Krous, MD; Hannah C. Kinney, MD

JAMA. 2006;296:2124-2132.

Context The serotonergic (5-hydroxytryptamine [5-HT]) neurons in the medulla oblongata project extensively to autonomic and respiratory nuclei in the brainstem and spinal cord and help regulate homeostatic function. Previously, abnormalities in 5-HT receptor binding in the medullae of infants dying from sudden infant death syndrome (SIDS) were identified, suggesting that medullary 5-HT dysfunction may be responsible for a subset of SIDS cases.

Objective To investigate cellular defects associated with altered 5-HT receptor binding in the 5-HT pathways of the medulla in SIDS cases.

Design, Setting, and Participants Frozen medullae from infants dying from SIDS (cases) or from causes other than SIDS (controls) were obtained from the San Diego Medical Examiner's office between 1997 and 2005. Markers of 5-HT function were compared between SIDS cases and controls, adjusted for postconceptional age and postmortem interval. The number of samples available for each analysis ranged from 16 to 31 for SIDS cases and 6 to 10 for controls. An exploratory analysis of the correlation between markers and 6 recognized risk factors for SIDS was performed.

Main Outcome Measures 5-HT neuron count and density, 5-HT_{1A} receptor binding density, and 5-HT transporter (5-HTT) binding density in the medullary 5-HT system; correlation between these markers and 6 recognized risk factors for SIDS.

Results Compared with controls, SIDS cases had a significantly higher 5-HT neuron count (mean [SD], 148.04 [51.96] vs 72.56 [52.36] cells, respectively; $P < .001$) and 5-HT neuron density ($P < .001$), as well as a significantly lower density of 5-HT_{1A} receptor binding sites ($P \leq .01$ for all 9 nuclei) in regions of the medulla involved in homeostatic function. The ratio of 5-HTT binding density to 5-HT neuron count in the medulla was significantly lower in SIDS cases compared with controls (mean [SD], 0.70 [0.33] vs 1.93 [1.25] fmol/mg, respectively; $P = .001$). Male SIDS cases had significantly lower 5-HT_{1A} binding density in the raphé obscurus compared with female cases (mean [SD], 16.2 [2.0] vs 29.6 [16.5] fmol/mg, respectively; $P = .04$) or with male and female controls combined (mean [SD], 53.9 [19.8] fmol/mg; $P = .005$). No association was found between 5-HT neuron count or density, 5-HT_{1A} receptor binding density, or 5-HTT receptor binding density and other risk factors.

Conclusions Medullary 5-HT pathology in SIDS is more extensive than previously delineated, potentially including abnormal 5-HT neuron firing, synthesis, release, and clearance. This study also provides preliminary neurochemical evidence that may help explain the increased vulnerability of boys to SIDS.