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COMMENTARY

Familial Small Upper Airways and Sleep-Disordered Breathing: Relationship to Idiopathic Apparent-Life-Threatening Events

Commentary on the article by Guilleminault *et al.* on page 14

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There are no diagnostic tests to confirm or rule out an idiopathic apparent life-threatening event (ALTE) and diagnosis is based solely on caretaker report (1–4). These episodes can occur during active or quiet sleep or while awake, and some are associated with feeding. There is no consensus definition, resulting in marked inter-study heterogeneity. The prevalence of ALTE is unknown.

Sixty-two of all ALTE in a large series were explained by digestive, neurologic, respiratory, cardiovascular, metabolic, unintentional, infectious, or intentional causes (1). The other 38% were idiopathic and 39% of these received vigorous stimulation or resuscitation.

Idiopathic ALTE have been evaluated for the presence of cardiorespiratory control abnormalities (2–3). No meta-analyses can be done, however, due to variable inclusion criteria and methods. The abnormalities observed include prolonged sleep apnea, excess periodic breathing, deficient ventilatory responsiveness to hypercarbia or hypoxia, fewer spontaneous arousals from sleep, deficient arousal responsiveness to hypercarbia or hypoxia, autonomic dysfunction, hypoxemic episodes, decreased heart rate variability, and dynamic soft tissue laryngeal obstruction associated with mixed and obstructive apnea (2–5). ALTE associated with these abnormalities are typically sleep-related (3). Among ALTE referred for evaluation, probably <50% have an identified abnormality in cardiorespiratory control and some studies have not shown any differences from healthy infants (3).

There is no consensus as to the extent of relationship between idiopathic ALTE and sudden infant death syndrome (SIDS), but <10% of ALTE have been reported to later die of SIDS and <10% of SIDS have had a prior ALTE (3). SIDS victims and ALTE have comparable epidemiologic risk factors (1). Families with obstructive sleep apnea are more likely to have family members with SIDS/ALTE than control families (6), and infants in families with multiple histories of SIDS, ALTE, and obstructive sleep apnea are more likely to have obstructive sleep apnea than families with only one case of SIDS or ALTE (7). These studies linking SIDS, ALTE and obstructive sleep apnea are provocative, but it is likely not valid to consider SIDS/ALTE as a combined outcome except insofar as both are related to the same pathophysiology. Some SIDS cases are likely associated with mechanisms unrelated to airway patency or to brainstem-mediated cardiorespiratory control and arousal (2, 3).

The report by Guilleminault *et al.* of sleep-disordered breathing (SDB) in infants with an ALTE and their families is also provocative and may provide further evidence of one mechanism for ALTE and one potential long-term outcome in older children and adults who had an ALTE during infancy (8). Among the 57% of ALTE with SDB, 43% of family members but only 7% of controls had been treated for SDB. They conclude that some ALTE occurrences may be the first indication of a SDB syndrome, and that genotypes associated with upper airway dysmorphia can result in an ALTE.

This large 3-generation family study includes a sleep/wake questionnaire and serial clinical evaluation of all 348 ALTE and 97% of parents, 71% of grandparents and 98% of siblings. Clinical assessment includes facial and oropharyngeal dimensions. The nocturnal polygraphic recordings include sleep state, central, mixed and obstructive apnea, and hypopnea. To assess "obstructive breathing," an esophageal catheter was placed for measurement of upper airway resistance, a measurement not previously reported in infants.

Limitations

The authors discuss limitations related to participation rates, racial and ethnic referral bias, and possible overrepresentation of SDB among ALTE referred to this sleep disorders center. They do not define SDB, but this term can be used to encompass any combination of central apnea, obstructive apnea, hypopnea, and increased upper airway resistance (9). Another limitation is absence of a definition for ALTE. There is no specified minimum severity threshold and no information regarding extent of evaluation to exclude explained ALTE. Relationship of the presenting symptoms to sleep state and feeding is not described. It would also be informative to know

to what extent clinical history differed in those with and without SDB, including exposure to cigarette smoke, and whether those with SDB typically presented with sleep-related symptoms.

Another limitation is the lack of quantitative data from the polygraphic recordings. The recordings have been dichotomized into normal or abnormal for the familial aggregation analyses. It would have been helpful to have more data regarding arousal criteria and the distribution and severity of central, mixed and obstructive apnea and hypopnea. "Obstructive apnea" without apnea/hypopnea is a unique and potentially important new criterion for SDB and more information about inspiratory effort, arousal, "Pes reversal," and "crescendo pattern" is needed.

The authors use the terms "upper airway anomalies" and "small upper airways" to refer to "cranio-facial-maxillomandibular" anatomic traits. These traits are exclusively upper airway and can be quantified by morphometric measurements using calipers or cephalometric radiographs ((5, 8, 10). They report an association between smaller upper airways and increased frequency of allergies. Insufficient details about definition and ascertainment notwithstanding, why would infants with SDB have an increased incidence of reported allergies?

The authors offer no hypotheses regarding allergies. The frequency of obstructive sleep apnea in children with habitual snoring, however, is increased in those with documented allergic sensitization (positive RAST) (11). These authors speculate that upper airway allergy leads to nasal edema, increased secretions, and to increased nasal airway resistance. A history of sinus problems/hay fever has also been observed to be an independent risk factor for SDB in children ((8, 12).

Although asthma is associated with (reactive) *lower airways*, Guilleminault *et al.* also report an association between smaller upper airways and increased incidence of asthma (8). They speculate that anatomically small upper airways may somehow contribute to risk for nocturnal asthma, but no mechanisms are proposed. A history of wheezing in children and adolescents from families with obstructive sleep apnea, however, is independently predictive of SDB even though forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) are not significantly lower ((8, 12). Lower airway resistance (maximum flow at FRC) is increased in infants with severe ALTE, however, supporting a possible role for reduced small airway patency in the pathogenesis of ALTE (13).

Implications

The major implication is that some ALTE are part of a "SDB syndrome" in families with small upper airways and that the genetic factors leading to small upper airways and symptomatic SDB as adults can also lead to ALTE during infancy. Since history of an ALTE may be associated with increased risk for SIDS (2, 3), does this mean that "genetic factors leading to small upper airways" are also relevant to SIDS?

Obstructive apnea has been identified in later SIDS victims (14), and infants in families with multiple cases of SIDS, ALTE, and obstructive sleep apnea are more likely to have obstructive apnea than infants in families with just one case of SIDS or ALTE (7). These mixed and obstructive apneas have generally been attributed to neuromuscular control of upper airway patency (2, 3). The only evidence for smaller upper airways in SIDS victims due to anatomic factors is a single report of retroposition of the maxilla (15) and of larger tongues (16) compared with controls. Terminal home memory monitor recordings are available in some SIDS victims, but not with breath detection methods capable of identifying obstructive apnea/hypopnea or increased upper airway resistance (17). Pending additional studies, therefore, one cannot extrapolate these observations in ALTE (8) to SIDS victims.

Future studies need to be more precise in defining pathogenesis of obstructive apnea or SDB among infants and older children. Airway obstruction related to impaired neuromuscular control of upper airway patency might have very different associations than similar degrees of obstruction related to adenotonsillar hypertrophy (soft tissue) or to bony tissue "cranio-facial-maxillomandibular" limitations. It is possible that some of the apparent but poorly-understood associations between obstructive sleep apnea, allergy, sinus problems/hay fever, wheezing and asthma, and upper/lower airway infections can be better understood if subjects are subclassified according to the extent of soft and bony tissue causes of upper airway obstruction.

Although environmental factors are important ((8, 18–21), smaller cranio-facial-maxillo-mandibular dimensions in infants and adult relatives with SDB also appear to have a genetic basis ((8, 22, 23). By using the tools of the Human Genome Project, it is now possible to address the molecular basis for a rapidly increasing array of clinical disorders (24–26). It is very unlikely that SDB, ALTE, or SIDS will be associated with single gene abnormalities or that clinical outcome will be determined by specific genotypes. As in many other clinical disorders, the genetic influences will almost certainly be polygenic, with multiple genes interacting in complex ways in different environments. Specific genotypes resulting in small upper airways (8) or impaired cardiorespiratory control (2, 3), for example, may seldom determine one's destiny to develop SDB, ALTE or SIDS, but could enhance susceptibility when exposed to environmental influences such as prone sleeping and cigarette smoking (3).

Specific genes potentially relevant to SDB, ALTE, and SIDS have been linked to abnormal cardiorespiratory control and sleep but not yet to development of the upper airway. Abnormalities in regulation of sleep and circadian rhythmicity are intimately related to cardiorespiratory integration and arousal responsiveness from sleep, and homologous counterparts of essential circadian clock genes in Drosophila have been identified in mammals (27, 28). Newborn mice lacking functional brain-derived neurotrophic factor (BDNF) exhibit ventilatory depression and deficient or absent hypoxic ventilatory drive (29). Hypoxic ventilatory drive appears to be dependent on the presence and activation of platelet-derived growth factor receptors (30).

Null mutants for Krox-20, a homeobox gene that appears necessary for normal development of the respiratory central pattern generator, exhibit an abnormally slow respiratory rhythm that could lead to life-threatening apnea (31). The ret proto-oncogene is important for development of brainstem muscarinic cholinergic pathways involved with responsiveness

to CO_2 and knockout mice have a depressed ventilatory response to hypercarbia (32). Diminished ventilatory responsiveness to hypercarbia has also been demonstrated in male newborn mice heterozygous for Mash-1 (33). There is a molecular link between ret and Mash-1, and the latter is expressed first in embryonic brainstem locus ceruleus neurons, an area involved with arousal responsiveness. Linkage of Mash-1 effects on ventilatory control with the X chromosome identifies one possible genetic basis for the impaired arousal responsiveness thought to be critically important in the pathophysiology of SIDS and for the higher risk in males (2, 3).

The studies of ventilatory control genotypes in animals are complemented by postmortem neurotransmitter studies in SIDS victims. There is significantly reduced binding to kainate receptors in the arcuate nucleus, a region of the human ventral medullary surface putatively involved in chemosensitivity to CO_2 (34). This could contribute to failed response to cardiorespiratory challenges during sleep and hence to sudden death. SIDS victims also have deficient serotonergic receptor binding in the brainstem (35), which would likely contribute to deficient arousal responsiveness from sleep as well as impaired regulation of breathing, heart rate, and body temperature.

Impaired ventilatory control has been associated with familial aggregation of SDB, SIDS, and ALTE. Asymptomatic adult offspring of patients with SDB appear to inherit subtle defects in ventilatory control that reduce ability to compensate for increased loads and maintain upper airway patency during sleep (36). These defects in family members suggest a propensity for dynamic airway narrowing that could complement or exacerbate cranio-facial-maxillo-mandibular limitations as causes of small upper airways (8).

In summary, this large multigenerational family study (8) suggests that SDB does aggregate in some families and that genotypes associated with small upper airways represent at least one mechanism for ALTE. Building on family studies such as this, genetic mechanisms need to be included as one research strategy in future studies of SDB and ALTE. SDB needs to be characterized in regard to impaired neuromuscular control of airway patency, soft tissue obstruction (*e.g.* adenotonsillar hypertrophy), and bony tissue limitations in upper airway patency. Standards need to be established for upper airway dimensions in healthy infants for comparison with infants at increased risk for ALTE and SIDS. Pending postmortem cephalometric radiographic studies in SIDS victims and appropriate controls, however, the percentage of SIDS cases associated with familial small upper airways is unknown.

REFERENCES

1. Kahn A, Rebuffat E, Franco P, N'Duwimana M, Blum D 1992 Apparent life-threatening events and apnea of infancy. In: Beckerman RC, Brouillette RT, Hunt CE (eds) Respiratory Control Disorders in Infants and Children. Williams & Wilkins, Baltimore, pp 178–189
2. Hunt CE 1992 The cardiorespiratory control hypothesis for sudden infant death syndrome. Clin Perinatol 19:757–771
3. Hunt CE 1996 Apnea and SIDS. In Kligman RM, Nieder ML, Super DM (eds) Practical Strategies in Pediatric Diagnosis and Therapy. W.B. Saunders Co., Philadelphia, pp 135–147
4. Poets CF, Samuels MP, Noyes JP, Hewertson J, Hartmann H, Holder A, Southall DP 1993 Home event recordings of oxygenation, breathing movements, and heart rate and rhythm in infants with recurrent life-threatening events. J Pediatr 123:693–701
5. Ruggins NR, Milner AD 1993 Site of upper airway obstruction in infants following an acute life-threatening event. Pediatr 91:595–601
6. Tishler PV, Redline S, Ferrette V, and Hans MG 1996 The association of sudden unexpected infant death with obstructive sleep apnea. Am J Resp Crit Care Med 153:1857–1863
7. McNamara F, Sullivan CE 2000 Obstructive sleep apnea in infants: relation to family history of sudden infant death syndrome, apparent life-threatening events, and obstructive sleep apnea. J Pediatr 136:318–323
8. Guilleminault C, Pelayo R, Leger D, Philip P, Ohayon M 2001 Sleep disordered breathing an upper airway anomalies in first degree relatives of ALTE children. Pediatr Res 50:14–22
9. Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research 1999 The report of the American Academy of Sleep Medicine Task Force. Sleep 22:667–689
10. Kushida CA, Efron B, Guilleminault C 1997 A predictive morphometric model for the obstructive sleep apnea syndrome. Ann Intern Med 127:581–587
11. McColley SA, Carrol JL, Curtis S, Loughlin GM, Sampson HA 1997 High prevalence of allergic sensitization in children with habitual snoring and obstructive sleep apnea. Chest 111:170–173
12. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G 1999 Risk factors for sleep disordered breathing in children: associations with obesity, race and respiratory problems. Am J Resp Crit Care Med 159:1527–1532
13. Hartman H, Seidenberg, Noyes JP, O'Brien L, Poets CF, Samuels MP, Southall DP 1998 Small airway patency in infants with apparent life-threatening events. Eur J Pediatr 157:71–74
14. Kahn A, Grosswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, Franco P, Bochner A, Alexander M, Bachy A, et al 1992 Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. Sleep 15:287–292
15. Rees K, Wright A, Keeling JW, and Douglas NJ 1998 Facial structure in the sudden infant death syndrome. BMJ 317:179–180
16. Siebert JR, Haas JE 1991 Enlargement of the tongue in sudden infant death syndrome. Pediatr Pathol 11:813–826
17. Meny RG, Carroll JL, Carbone MT, Kelly DH 1994 Cardiorespiratory recordings from infants dying suddenly and unexpectedly at home. Pediatr 93:44–49
18. Harvold EP 1968 The role of function in the etiology and treatment of malocclusion. Am J Orthod 54:883–898
19. Tomer BS, Harvold EP 1982 Primate experiments on mandibular growth direction. Am J Orthod 82:114–119
20. Miller A, Vargervik K, Chierici G 1984 Experimentally induced neuromuscular changes during and after nasal airway obstruction. Am J Orthod 85:385–392
21. Vargervik K, Harvold EP 1987 Experiments on the interaction between oro-facial function and morphology. Ear Nose Throat J 66:201–208
22. Kraus BS, Wise WJ, Frei RH 1959 Heredity and the cranio-facial complex. Am J Orthod 45:172–217
23. Holland PW 1988 Homeobox genes and the vertebrate head. Development 103:17–24
24. American Thoracic Society Finding genetic mechanisms in syndromes of sleep disordered breathing. Available at: http://www.thoracic.org/statements/sleepdisorder/sleep. Accessed July, 2000
25. Han F, Strohl KP 2000 Inheritance of ventilatory behavior in rodent models. Resp Physiol 121:247–256
26. Holtzman NA, Marteau TM 2000 Will genetics revolutionize medicine? N Engl J Med 343:141–144
27. Schibler U, Tafti M 1999 Molecular approaches towards the isolation of sleep-related genes. J Sleep Res 8(suppl 1):1–10
28. Tafti M, Chollet D, Valatx JL, Franken P 1999 Quantitative trait loci approach to the genetics of sleep in recombinant inbred mice. J Sleep Res 8(suppl 1):37–43
29. Katz DM, Balkowiec A 1997 New insights into the ontogeny of breathing from genetically engineered mice. Curr Opinion Pul Med 3:433–439
30. Gozal D, Gozal E, Simakajornboon N 2000 Signaling pathways of the acute hypoxic ventilatory response in the nucleus tractus solitarius. Respir Physiol 121:209–221
31. Jacquin TD, Borday V, Schneider-Maunoury S, Topilko P, Ghilini G, Kato F, Charmay P, Champagnat J 1996 Reorganization of pontine rhythmogenic neuronal networks in Krox-20 knockout mice. Neuron 17:747–758
32. Burton MD, Kawashima A, Brayer JA, Kazemi H, Shannon DC, Schuchardt A, Costantini F, Pachnis V, Kinane TB 1997 RET proto-oncogene is important for the development of respiratory CO2 sensitivity. J Auto Nerv System 63:137–143
33. Dauger S, Renolleau S, Vardon G, Nepote V, Mas C, Simonneau M, Gaultier C, Gallego J 1999 Ventilatory responses to hypercapnea and hypoxia in Mash-1 heterozygous newborn and adult mice. Pediatr Res 46:535–542
34. Panigrahy A, Filiano JJ, Sleeper LA, Mandell F, Valdes-Dapena M, Krous HF, Rava LA, White WF, Kinney HC 1997 Decreased kainate receptor binding in the arcuate nucleus of the sudden infant death syndrome. J Neuropathol Exp Neurol 56:1253–1261
35. Panigrahy A, Filiano JJ, Sleeper LA, Kinney HC, White WF, Kinney HC 2000 Brainstem serotonergic receptor binding in the sudden infant death syndrome. J Neuropathol Exp Neurol 59:377–384
36. Pillar G, Schnall RP, Peled N, Oliven, Lavie P 1997 Impaired respiratory response to resistive loading during sleep in healthy offspring of patients with obstructive sleep apnea. Am J Respir Crit Care Med 155:1602–1608