Published in final edited form as:

Cleft Palate Craniofac J. 2017 November ; 54(6): 734–738. doi:10.1597/16-090.

Sleep Outcomes in Children With Single-Suture Craniosynostosis Compared With Unaffected Controls

Baiyang Sun, M.P.H. [Ph.D. student],

Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

Yona K. Cloonan, Ph.D. [Assistant Professor],

Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania

Brent R. Collett, Ph.D. [Associate Professor],

Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington; Center for Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, Washington

Matthew L. Speltz, Ph.D. [Professor]

Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington; Center for Child Health, Behavior and Development, Seattle Children's Research Institute, Seattle, Washington

Abstract

Objective: To compare risk for sleep-disordered breathing between children with and without single-suture craniosynostosis.

Participants: A total of 184 children with single-suture craniosynostosis and 184 controls.

Main Outcome Measures: Parent reported sleep-disordered breathing–related symptoms.

Results: Current sleep problems were reported in 19% of patients with single-suture craniosynostosis and 14% of controls (adjusted odds ratio = 1.6; 95% CI, 0.9 to 2.8). Ever having sleep problems was reported in 25% and 23% of cases and controls, respectively (adjusted odds ratio = 1.2; 95% CI, 0.7 to 1.9). Overall, snoring was statistically associated with single-suture craniosynostosis ($P = .01$) and was more often reported as 2+ nights per week (versus never) in patients with single-suture craniosynostosis (13%) than in controls (4%) (adjusted odds ratio = 3.5; 95% CI, 1.5 to 8.2).

Conclusions: Though preliminary, increased presence of snoring during sleep in children with single-suture craniosynostosis compared with controls suggests that children with isolated single-suture craniosynostosis may be at increased risk for sleep-disordered breathing. Further study using standardized assessments of sleep-disordered breathing is needed.

Keywords

child; craniofacial abnormalities; craniosynostoses; sleep apnea syndromes; sleep disorders

Craniosynostosis is a craniofacial anomaly involving premature fusion of one or more cranial sutures during the perinatal period. Isolated single-suture craniosynostosis (SSC), which affects a single suture and occurs without other congenital anomalies, is the most prevalent type (Ursitti et al., 2011; Garza and Khosla, 2012). Although estimates vary, overall prevalence of craniosynostosis ranges from 3 to 14 per 10,000 live births. Single-suture craniosynostosis with any suture involved is present in approximately 5 per 10,000 live births (Shuper et al., 1985; Singer et al., 1999).

Sleep-disordered breathing (SDB) refers to several chronic conditions categorized by partial or complete breathing obstruction during sleep, ranging from primary snoring to obstructive sleep apnea (Gaultier, 1995). Snoring is the most common and recognizable manifestation (Sinha and Guilleminault, 2010). Studies indicate that childhood SDB is not only associated with behavioral and neurocognitive problems, such as decreased attention, learning difficulties, and anxiety/depression symptoms, but also with long-term cardiovascular consequences (Chervin et al., 2002; O'Brien et al., 2004; Tran et al., 2005; Capdevila et al., 2008; O'Brien, 2011).

Previous studies have indicated that children with craniofacial anomalies face a higher risk of SDB as compared with unaffected children; however, the literature is sparse and focuses on cleft lip/palate, craniofacial microsomia, and syndromic craniosynostosis (Cloonan et al., 2009; MacLean et al., 2009; Al-Saleh et al., 2011; Robison and Otteson, 2011; Plomp et al., 2012). Few published studies have examined sleep outcomes in children with nonsyndromic craniosynostosis. One previous study indicated that 50% of children with nonsyndromic craniosynostosis had SDB (Alsaadi et al., 2013); however, small sample size, possible referral bias, and lack of a comparison group limit interpretation. To our knowledge, no studies have compared sleep outcomes in children with and without isolated SSC. We therefore sought to evaluate the potential association between isolated SSC and SDB, based on parent report of SDB-related symptoms.

METHODS

This cross-sectional study includes participants in a multi-site follow-up study of neurodevelopment in children with and without isolated SSC (Speltz et al., 2007; Starr et al., 2007). During initial enrollment, cases were infants diagnosed with isolated SSC (sagittal, metopic, right unicoronal, left unicoronal, or lambdoid). Controls were healthy infants without congenital anomalies and were matched to the case group by age, sex, race/ethnicity, and family socioeconomic status (SES). Informed consent was obtained before enrollment, with institutional review board approval at each site.

At follow-up, demographic characteristics and medical history were obtained by staff-administered interview. Supplemental questions about SDB-related symptoms were also assessed at this school-age visit. Parents were asked whether their child had new or ongoing sleep problems since the previous study visit. Among those who responded yes, the frequency (*usually*: 5 to 7 nights per week, *sometimes*: 2 to 4 nights per week, *rarely*: 0 to 1 nights per week, and *never*) of six SDB symptoms were further assessed, including restless sleep, arousal, snoring, snorting/gasping, apneas, and daytime sleepiness.

Statistical Analysis

Descriptive analyses were used to illustrate the sociodemographic characteristics of children with and without SSC and according to suture type. Counts and percentages were calculated for discrete variables; means, standard deviations, and ranges were calculated for continuous variables. Logistic regression was conducted for binary variables to compare the odds of (1) current and (2) ever sleep problems between cases and controls. Multinomial logistic regression was used for analysis of snoring (*never, 0 to 1 nights per week, 2+ night per week*). All models included sex, race/ethnicity (non-Hispanic white, other), age, and SES as covariates (Redline et al., 1999; Urschitz et al., 2004; Lumeng and Chervin, 2008). Proportions of snoring frequency responses were compared across suture type using the Fisher exact test.

In addition, separate sensitivity analyses for regression models were conducted by excluding children who had probable and known causal mutations for SSC ($n = 18$), suffered from respiratory conditions (asthma and respiratory infections) ($n = 38$ SSC and 31 controls), and had past airway interventions (tonsillectomy and adenoidectomy) ($n = 15$ SSC and 16 controls). Finally, because maternal smoking during pregnancy is more common for children with SSC (Hackshaw et al., 2011) and may be associated with childhood SDB (Calhoun et al., 2010; Li et al., 2010), we added maternal smoking during pregnancy (yes/no) as a covariate in the multivariable regression models.

All aforementioned analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Participants included 184 children with isolated SSC and 184 unaffected controls, with mean ages of 7.5 and 7.4 years, respectively (Table 1). In the SSC and control groups, respectively, the majority of children were boys (64% and 63%), were non-Hispanic white (77% and 67%), and had high family SES (Hollingshead Classification I or II; 71% and 85%). Sagittal (42%) and lambdoid (7%) were the most and least common synostoses among cases, respectively. Race/ethnicity and age were similar across suture types. There were more girls among children with left (77%) and right (54%) unicoronal SSC but more boys for other types. The composition of family SES was similar overall, though the proportion of children with high family SES (I or II) in the left unicoronal group (55%) was lower than in the others.

SDB-Related Outcomes

Current sleep problems were reported slightly more often in children with SSC (19%) than in controls (14%; adjusted odds ratio [aOR] = 1.6; 95% CI, 0.9 to 2.8) (Table 2). There was no difference in report of having ever had sleep problems between cases (25%) and controls (23%; aOR = 1.2; 95% CI, 0.7 to 1.9).

The overall association between SSC and snoring was statistically significant ($P = .01$) in the multinomial logistic regression model. Snoring was more often reported as 2+ nights per week by parents of children with SSC (13%) than of controls (4%) (aOR versus never = 3.5; 95% CI, 1.5 to 8.2) and was reported as 0 to 1 night per week for 5% and 8% of children

with SSC and of controls, respectively (aOR versus never = 0.8; 95% CI, 0.3 to 1.9) (Table 3).

Eight children with left unicoronal SSC (37%) were reported as having snoring symptoms (0 to 1 nights per week or 2+ nights per week), followed by sagittal (13; 17%), lambdoid (2; 17%), metopic (7; 14%), and right unicoronal (2; 8%) (not shown). Overall comparison of snoring frequency across suture types was not statistically significant ($P = .52$).

sensitivity Analyses

After excluding 18 children with identified genetic mutations associated with craniosynostosis, the odds ratio of snoring 2+ nights per week between children with SSC and controls decreased somewhat (aOR versus never = 2.9; 95% CI, 1.2 to 7.1). Remaining sensitivity analyses were comparable to those in the full sample.

DISCUSSION

Unlike syndromic craniosynostosis, SSC usually does not involve midface deficiency, which is thought to be the principal risk factor for SDB among children with craniofacial anomalies (Cielo and Marcus, 2015). However, in a 2012 study, SDB was present in 50% of children with isolated craniosynostosis, with no association between occurrence of SDB and suture number involved (Alsaadi et al., 2013). Without a comparison group, that study did not address whether children with SSC had a higher risk for SDB than unaffected controls. Our study found a higher presence of parent-reported snoring among children aged 7 to 11 years with SSC compared with controls. Though preliminary, our results suggest that children with isolated SSC may have a higher risk for SDB, which is consistent with previous studies of other craniofacial anomalies (Cloonan et al., 2009; MacLean et al., 2009; Al-Saleh et al., 2011; Robison and Otteson, 2011; Plomp et al., 2012). To our knowledge, our study was the first to compare the occurrence of SDB between children with and without isolated SSC. Moreover, the multicenter design allowed for a relatively large number of children with isolated SSC and is a strength of our study.

Furthermore, our study compared both the single snoring symptom and the generic indicators of current/ever sleep problems between SSC and controls. Diverse manifestations of SDB are present for children, such as nighttime snoring, daytime sleepiness, restless sleep, frequent arousals, snorting/gasping, witness apneas, and dry mouth/mouth breathing (Sinha and Guilleminault, 2010). The constellation of symptoms changes with age; yet, nighttime snoring is regarded as the most common presentation of SDB at any age among children. For our results, though parent-reported snoring alone is insufficient to diagnose SDB, increased presence of frequent snoring is a sign of higher risk for SDB among children with SSC. No significant difference in current/ever sleep problems may be explained by including low-frequency or nonspecific symptoms.

Polysomnography is the criterion standard for diagnosis of SDB, but utilization is limited by high price and time burden in large pediatric epidemiological studies. Thus, validated parent-report questionnaires are commonly used to identify suspected SDB (Spruyt and Gozal, 2011). One important limitation of this study is that we did not use a standardized

and validated questionnaire of SDB (e.g., Pediatric Sleep Questionnaire; Archbold et al., 2002). Moreover, given that parent-reported symptoms largely depend on parental awareness and sleep habits (e.g., cosleeping), supplemental questions for parent awareness are needed to assess whether parents of participants with isolated SSC have closer observation for their children during sleep than parents of controls do. We also lacked height and weight and were therefore unable to adjust for body mass index—a known risk factor for SDB—in our analysis.

Both maternal smoking during pregnancy and passive smoking exposure are risk factors for pediatric SDB (Li et al., 2010). Though parental smoking status was not collected at follow-up, maternal smoking status during pregnancy was included as a covariate in our sensitivity analyses and did not affect appreciably the association between SSC and SDB.

Sleep-disordered breathing, even primary snoring, can result in neurocognitive impairment among children (Gozal and Pope, 2001; Brockmann et al., 2012a; Brockmann et al., 2012b); yet, SDB is a treatable condition using nonsurgical and/or surgical therapies (Guilleminault, 2005; Cielo and Marcus, 2015). Thus, early diagnosis and treatment are important. Our preliminary study may have implications for clinical care for SDB in an already-vulnerable pediatric population. Further study using standardized questionnaires or polysomnography should be conducted to confirm the association between SSC and SDB. At this point, screening of sleep problems in children with isolated SSC should be performed as part of routine care, with heightened awareness that their risk may be higher than the general population.

Acknowledgments.

We thank all participants in the Child and Infant Learning Project. Also, we would like to thank the study coordinators, data collection staffs, and data management staffs for their contribution to this study.

This study was supported by the National Institute for Dental and Craniofacial Disorders of the National Institutes of Health (R01DE013813). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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TABLE 1

Sociodemographic Characteristics of SSC Cases and Controls at Follow-Up

	Controls, n (%) [*]	Isolated SSC, n (%)				
		All SSC	Sagittal	Metopic	Right Unicoronal	Left Unicoronal
N	184	184	77 (42)	49 (27)	24 (13)	22 (12)
Age, years						
Mean (SD)	7.4 (0.5)	7.5 (0.6)	7.5 (0.7)	7.4 (0.3)	7.4 (0.3)	7.4 (0.3)
Range	7.0: 11.1	6.9: 11.5	7.0: 11.5	7.0: 8.4	7.0: 8.5	6.9: 8.1
Sex						
Female	69 (38)	67 (36)	18 (23)	14 (29)	13 (54)	17 (77)
Male	115 (63)	117 (64)	59 (77)	35 (71)	11 (46)	5 (23)
Race [‡]						
White	137 (77)	148 (86)	64 (89)	38 (81)	20 (87)	16 (84)
Black	12 (7)	9 (5)	2 (3)	5 (11)	1 (4)	1 (5)
Asian/Pacific Islands	4 (2)	6 (3)	0 (0)	3 (6)	0 (0)	2 (11)
Other	24 (14)	9 (5)	6 (8)	1 (2)	2 (9)	0 (0)
Hispanic	22 (12)	21 (11)	10 (13)	5 (10)	1 (4)	3 (14)
SES [‡]						
I: 55–60 (high)	54 (29)	44 (24)	21 (27)	11 (22)	3 (13)	5 (23)
II: 40–54	103 (56)	86 (47)	33 (43)	24 (49)	17 (71)	7 (32)
III: 30–39	14 (8)	32 (17)	13 (17)	9 (18)	3 (13)	4 (18)
IV: 20–29	10 (5)	20 (11)	10 (13)	4 (8)	1 (4)	5 (23)
V: 8–19 (low)	3 (2)	2 (1)	0 (0)	1 (2)	0 (0)	1 (5)
Site						
Seattle	72 (39)	76 (41)	34 (44)	20 (41)	6 (25)	12 (55)
Chicago	76 (41)	66 (36)	16 (21)	21 (43)	14 (58)	10 (45)
St. Louis	9 (5)	17 (9)	12 (16)	1 (2)	3 (13)	0 (0)
Atlanta	27 (15)	25 (14)	15 (19)	7 (14)	1 (4)	0 (0)

^{*} Percentages may not add up to 100% due to rounding.[‡] Race was missing for seven controls and 12 SSC cases, all of whom were Hispanic.

SES = socioeconomic status, Hollingshead Four Factor Index of social status (Hollingshead, 1975),[‡]

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TABLE 2
Results of Logistic Regression Comparing the Odds of Current and Ever Sleep Problems in SSC Cases Versus Controls

	Control, n (%)	SSC, n (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)*	P Value [†]
Current sleep problem					
No	159 (86)	149 (81)	1.5 (0.8, 2.5)	1.6 (0.9, 2.8)	.12
Yes	25 (14)	34 (19)			
Ever sleep problem					
No	142 (77)	138 (75)	1.1 (0.7, 1.8)	1.2 (0.7, 1.9)	.58
Yes	42 (23)	45 (25)			

* Adjusted for sex, age, race/ethnicity, and family SES.

[†] P-value based on the adjusted regression models.

TABLE 3

Results of Multinomial Logistic Regression to Assess the Association Between Snoring and SSC

Parent Reported Frequency of Snoring	Control, n (%)	SSC, n (%)	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) [*]	P Value [†]
Never	161 (88)	149 (82)	Referent	Referent	–
0–1 nights/week	14 (8)	9 (5)	0.7 (0.3, 1.7)	0.8 (0.3, 1.9)	.59
2+ nights/week	8 (4)	23 (13)	3.1 (1.3, 7.2)	3.5 (1.5, 8.2)	<.01

^{*} Adjusted for sex, age, race/ethnicity and family SES.[†] P-value based on the adjusted regression models. $P = .01$ for the overall multinomial regression model based on Wald test.