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Ear Infection in Isolated Cleft Lip: Etiological Implications

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Abstract

Background and Hypothesis—Chronic ear infections are a common occurrence in children with orofacial clefts involving the secondary palate. Less is known about the middle ear status of individuals with isolated clefts of the lip, although several studies have reported elevated rates of ear infection in this group. The purpose of this retrospective study was to test the hypothesis that chronic ear infections occur more frequently in isolated cleft lip cases (n=94) compared with controls (n=183).

Methods—A questionnaire was used to obtain information on history of chronic ear infection. The association between ear infection status (present/absent) and cleft lip status (cleft lip case/control) was tested using both chi-square and logistic regression.

Results and Conclusions—The reported occurrence of chronic ear infection was significantly greater in cleft lipcases (31%) compared to unaffected controls (11%). After adjusting for age and sex, having a cleft lip increased the odds of being positive for ear infection by a factor greater than three (OR=3.698; 95%CI=1.91–7.14). Within cleft lipcases, there was no difference in the occurrence of ear infection by defect laterality or by the type of clefting present in the family history. Although velopharyngeal insufficiency was present in 18.4% of our cleft lip sample, there was no statistical association between ear infection and abnormal speech patterns. These results may have potential implications both for the clinical management of isolated cleft lip cases and for understanding the etiology of orofacial clefting.

Keywords

otitis media; ear infection; cleft lip; velopharyngeal insufficiency

INTRODUCTION

The association between chronic otitis media (OM) and orofacial clefts involving the secondary palate is well documented. Reported rates of OM in cleft lip and palate (CLP) and isolated cleft palate (CP) range from approximately 70% (Sheahan et al., 2003; Flynn et al., 2009; Kwan et al., 2011; Chen et al., 2012) to well over 90% (Paradise et al., 1969; Dhillon, 1988). There are several anatomical explanations for the association between palatal forms of clefting and the Eustachian tube dysfunction that leads to OM (reviewed in Kuo et al., 2013); these include misalignment of the palatal muscles responsible for opening the tube and intrinsic deficiencies in the tissues comprising the Eustachian tube. Due to the high rate of recurrent OM in clefts involving the secondary palate, early intervention is recommended in order to prevent potential hearing loss (Bluestone, 2004; Gani et al., 2012).

The propensity for OM in isolated cleft lip (CL) is less well understood, with only a handful of previous studies reporting contradictory results. Both Sheahan et al. (2003) and Kwan et al. (2011) found little evidence of increase risk of middle ear problems in CL cases. In contrast, Paradise et al. (1969) reported that 22% of CL cases had abnormal eardrums, while 33% had OM. Vallino et al. (2008) reported that 33% of their CL sample demonstrated OM, while 13% showed evidence of mild hearing loss. Most recently, Deedler et al. (2011) used questionnaires to assess acute OM in their patient population; they found that 32.5% of CL cases and 34% of CLA (cleft lip and alveolous) cases reported at least one instance of acute

OM, with the majority reporting two or more. Importantly, a sizable portion of this same CL/CLA sample reported speech deficits, including articulation and resonance problems. Thus, three independent studies using different methods of assessment have reported middle ear problems in approximately one-third of their CL cases. All three studies however failed to include a control group for comparison, so it is unclear if the reported rate in CL was outside of the normal range.

If CL cases are indeed at an increased risk for middle ear disease, this could have important implications for the clinical management of this less severe form of orofacial clefting. However, the potential implications for studies looking into the etiologic basis of orofacial clefting may be equally important. T he presence of middle ear problems, especially in concert with other markers of palatal dysfunction, could represent a sign of dysmorphology beyond the isolated lip(Vallino et al., 2008). In the present study, we test the hypothesis that the reported incidence of chronic ear infection will be higher in a sample of CL cases compared with healthy controls. Further, we will test the hypothesis that ear infection and velopharyngeal function are associated traits in CL cases.

MATERIALS AND METHODS

Information on ear infection status was available for 277 unrelated individuals: 94 probands with CL and 183 unaffected controls. Both cases and controls were limited to individuals of Caucasian ancestry (self-identified) age 18 years or younger. The mean age of the CL group was 7.4 years (±4.6), compared to 9.4 years (±5.2); this difference was statistically significant ($p = 0.002$). The CL group was comprised of58 males and 36 females, while the control group was comprised of 94 males and 89 females; the sex distribution did not differ statistically across the two groups ($p > 0.05$). CL cases were recruited as part of a large multi-center study of the genetics of orofacial clefting (Weinberg et al., 2006). Most were ascertained through either research registries or from populations served by craniofacial clinics. Cases were collected at six sites: Pittsburgh, Iowa City, Denver, St. Louis, Houston, and Budapest. A history of syndromic clefting was an exclusion criterion for cases. Unaffected controls with no prior personal or family history of craniofacial birth defects were recruited from the same general region as the cases, typically by targeted advertisement (e.g. flyers or news ads displayed throughout the communities where cases were seen), general research registries or word of mouth. Local ethics (IRB) approval was obtained at each collection site.

Following informed consent, both cases and controls were asked a series of questions about their health history. Since the individuals included in this study were under 18 years of age, at least one parent or guardian was present who was able to provide this information about their child. As part of this larger health survey, subjects or their parents were asked to report on their (or their child's) history of chronic ear infections and treatments (medications and ventilation tubes).

For the purposes of statistical analysis, subjects were classified simply as positive or negative for a history of ear infection. As an initial step, simple 2x2 Fisher's exact chi-square test was performed to test for an association between ear infection status (present/

absent) and cleft lip status (CL case/control). A logistic regression approach was then used to investigate whether cleft affection status was predictive of ear infection status. Both age and sex were entered in the logistic regression model in order to adjust for these potential confounders. By entering these predictors together in the model, the unique effects of affection status on ear infection status can be assessed after controlling for age and sex. Within the CL group, the proportion of ear infection was also compared between unilateral and bilateral CL cases. Further, by looking at the type of clefts present in additional family members (3rddegree relatives or closer) CL cases were assigned to a CL only family group (where only CL was present in the family history) or a CL/P family group (where some combination of CL and CLP was present) and the proportion of ear infection compared. These latter two comparisons were carried out using 2x2 Fisher's exact chi-square tests.

To further investigate the possibility that subtle palatal or pharyngeal abnormalities might be present in our CL case sample, the degree of trait concordance between velopharyngeal insufficiency (VPI) and ear infection was assessed. Trained speech language pathologists evaluated VPI using the Pittsburgh Weighted Speech Score (Dudas et al., 2006). Subjects with a score of three or greater were considered to have clinical VPI. VPI scores were only available for a small subset of the CL case sample (N = 38). A Fisher's exact chi-square test was conducted to evaluate the association between VPI (present/absent) and ear infection (present/absent).

Finally we examined the frequency of reported ear infection in an additional sample of 245 individuals with clinically confirmed CLP derived from the same populations. The frequency of reported infection in CLP cases was compared to both CL cases and controls using Fisher's exact chi-square tests.

All results were considered significant at $p \leq 0.05$. All analyses were completed using the statistical software package SAS v9.2. (SAS Institute Inc., Cary, NC).

RESULTS

The results of each chi-square test are presented in Table 1. The reported occurrence of chronic ear infection was significantly greater in CL cases compared to unaffected controls (31% versus 11%, respectively; $p < 0.001$). This result was further confirmed with logistic regression (Table 2); after adjusting for age and sex, having a cleft lip increased the odds of being positive for ear infection by a factor greater than three (OR = 3.698; 95% CI = 1.91 – 7.14). The variables sex and age were not found to be independently predictive of ear infection in our dataset. Within CL cases, there was no difference in the occurrence of ear infection by defect laterality or by the type of cleft family group (CL only versus CL/P), although as expected the frequency in cases from CL/P families was slightly higher (39% versus 26%). Furthermore, although VPI was present in 18.4% of our CL sample, there was no statistical association between ear infection and VPI (i.e., there was no concordance between the two traits). CLP cases had a 68% (171/245) reported occurrence of chronic ear infection; this was significantly higher than the rate observed in both CL cases ($p < 0.001$) and controls ($p < 0.001$). All results remained statistically significant after adjusting for multiple testing.

DISCUSSION

Our results show that individuals with nonsyndromic CL had a significantly higher reported rate of chronic ear infection than unaffected controls. The reported rate of ear infection in our CL sample was 31%. This figure is almost identical to the rate of OM reported in CL cases by previous studies(Paradise et al., 1969; Vallino et al., 2008; Deedler et al., 2011). While the observed rate of ear infection in our CL sample was high compared with controls, it was still greatly reduced compared to the very high rate generally associated with clefts involving the secondary palate (Paradise et al., 1969; Sheahan et al., 2003; Flynn et al., 2009; Kwan et al., 2011; Chen et al., 2012). This was confirmed in our sample as well. Due to the universally high rate reported in CLP and CP, it was predicted that CL cases from families with a history of secondary palatal involvement (CL/P families) would have a higher rate of ear infection than CL cases from families where only CL was present; this pattern was observed, but the difference did not reach statistical significance. Echoing the concern of others (Vallino et al., 2008; Deedler et al., 2011), these results suggest that CL cases should be monitored closely for signs of OM and hearing loss.

One explanation for the elevated rate of ear infection in CL cases is Eustachian tube dysfunction resulting from altered development of the secondary palate and/or its associated musculature. In some cases this could be due to an undiagnosed submucous cleft palate. Gosain et al. (1999), for example, confirmed submucous cleft palate (visible or occult) in 36% of their CL sample. In the absence of a definitive defect, another possibility is alteration of the size and shape of the hard and/or soft palate, the nasopharyngeal space, or the cranial base(reviewed in Ward et al., 2002). The lack of associated VPI in CL cases with ear infections would seem to cast doubt that intrinsic deficiencies in the palatal architecture are the root cause. However, VPI was only assessed at the time of participation in the study, meaning that in some individuals the speech problems may have resolved on their own or bee n mitigated by therapy earlier in life. Other studies have also failed to find a relationship between velopharyngeal function and middle ear status (da Silva et al., 2010). An alternative possible explanation is structural alteration of the Eustachian tube itself and its associated cartilages, which have been documented in cases of CP (reviewed in Bluestone, 2004). This could indicate a common etiologic basis for the CL and the morphological changes in the Eustachian tube-middle ear complex(Maguire et al., 2014). A rigorous and careful assessment of the soft palate status in our CL sample, in particular those cases demonstrating a history of OM or VPI or both, would allow for a more complete phenotypic picture to emerge and could help to determine whether subtle palatal defects might be implicated.

More comprehensive assessment of the phenotype is critical to studies on the genetic basis of clefting. The identification of potential palatal problems in cases of CL raises concerns about the classification used in genetic studies of the orofacial clefting. Although they did not occur together, this study found high rates of both ear infection and VPI in CL individuals with ostensibly structurally intact palates. These individuals may be etiologically more similar to CLP cases. This distinction is important as CL and CLP may have distinct genetic risk factors (Marazita et al., 2009; Ludwig et al., 2012), which could be obscured if the two groups are lumped together. Similar diagnostic uncertainty has been raised

previously with CP, where a subset of cases was found to possess subclinical upper lip defects identified via ultrasound (Weinberg et al., 2008).

The major weakness with the present study was the means of assessing ear infection. Information on ear infection was obtained via questionnaire only; no medical records were consulted and no physical examinations were conducted. In the context of this study, we were interested in the subject's entire health history, as opposed to their present status. Prior studies have also used questionnaires to assess middle ear status (Sheahan et al., 2003; Deedler et al., 2011). This approach, however, is susceptible to recall bias. It is also probable that some instances of middle ear disease were missed in both cases and controls, due to the fact that OM may be present without symptoms. Our questionnaire simply asked about a history of chronic ear infection. Subjects with asymptomatic OM would have likely answered this question in the negative. We were also not able to make a distinction between subtypes of OM, such as recurrent acute OM and chronic OM with effusion, which may be important to ascertain in this population. It is worth noting, however, that the rate of ear infection in our CL sample is almost identical to that reported by three previous studies (Paradise et al., 1969; Vallino et al., 2008; Deedler et al., 2011). Further, using this same medical history questionnaire in a sample of case s with CLP (n = 245), roughly 70% reported a history of ear infections – a figure in line with many reported estimates for clefts involving the secondary palate(Sheahan et al., 2003; Flynn et al., 2009; Kwan et al., 2011; Chen et al., 2012). These findings suggest that recall bias and issues of disease definition did not have a major effect on our dataset.

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Table 1

Tests of association between chronic ear infection and phenotypes of interests in CL cases.

	Ear Infection			
Comparison	**Present**	**Absent**	**Chi-Square**	**p**
By affection status				
CL case(n = 94)	29 (31%)	65 (69%)	16.928	< 0.001
Control(n = 183)	20 (11%)	163 (89%)		
By CL case laterality				
Unilateral(n = 85)	28 (33%)	57 (67%)	1.818	0.27
Bilateral(n = 9)	1 (11%)	8 (89%)		
By cleft family type				
CL only(n = 66)	18 (26%)	48 (74%)	1.330	0.33
CL/P(n = 28)	11 (39%)	17 (61%)		
By VPI status*				
VPI present (n = 7)	3 (43%)	4 (57%)	0.505	0.66
VPI absent (n = 31)	9 (29%)	22 (71%)		

*VPI scores only available for 38 CL subjects

Table 2

Logistic regression testing whether the presence of CL is predictive of reported chronic ear infection status.

Variable	b	se	Wald	p	OR (95% CI)
Affection Status	1.308	0.336	15.154	0.0001	3.698 (1.91–7.14)
Age	0.025	0.333	0.578	0.45	1.026 (0.96–1.10)
Sex	0.435	0.339	1.652	0.20	1.546 (0.80–3.00)
Constant	−2.582				

Outcome variable: ear infection (present/absent). Affection status: CL case or control. Overall logistic regression model is significant: Wald = 17.474; df = 3; p = 0.0006