Published in final edited form as:

Cleft Palate Craniofac J. 2016 September ; 53(5): 607–613. doi:10.1597/15-130.

Resolution of Otitis Media with Effusion in Children with Cleft Palate Followed Through 5 Years of Age

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Abstract

Objective—Describe the temporal pattern of otitis media with effusion (OME) resolution for a cohort of non-syndromic cleft palate children enrolled before palatoplasty and followed through 5 years of age.

Design—Prospective, longitudinal study of the time course for OME resolution in infants and children with palatal clefts.

Setting—Cleft Palate Craniofacial Center of a tertiary care pediatric hospital.

Participants—Fifty-two children with cleft palate, 29 Male, 45 White, Veau 1–4 who had a Furlow-type palatoplasty between 10 and 24 months of age done by 1 of 6 surgeons.

Interventions—Standard cleft palate management supplemented by study visits to the research clinic pre- and post-palatoplasty and then yearly to age 6 years for assessments of middle ear status by interval history, otoscopy and tympanometry.

Main Outcome Measure—Age at otitis media resolution defined as the age in years at the first in a sequence of “disease-free” diagnoses not interrupted or followed by any other diagnosis.

Results—For ears/subjects, the cumulative percent OME resolution for ears/children at ages <1, 1, 2, 3, 4, 5 years was 4.1/4.4, 14.3/10.9, 31.6/21.7, 45.9/37.0, 56.1/50.0 and 70.4/60.9%. OME-resolution followed a simple linear time-curve with slopes of 13.5% (CI=12.2–14.8%, $r^2=0.99$) and 11.9% (CI=10.1–13.6%, $r^2=0.99$) resolutions per year for ears and children, respectively.

Conclusions—There is a natural, age-related pattern of resolution for the persistent OME that affects most infants and young children with cleft palate that is not affected by palatoplasty.

Keywords

otitis media with effusion; cleft palate; prospective study; disease resolution

INTRODUCTION

Orofacial clefts including cleft lip (CL) and cleft palate (CP) are among the most common congenital abnormalities in humans with a prevalence of approximately 1.6/1000 live births (MMWR, 2006). Palatal clefts with/without cleft lip (CP±CL) adversely affect normal craniofacial growth and development leading to dysmorphologies in the dentition, face and cranial base, compromise velopharyngeal competence leading to poor speech, and greatly increase the risk for otitis media with effusion (OME) leading to mild to moderate conductive hearing losses when extant (Butow, 1984; Garcia Romero et al., 2004; Kreilborg et al., 2009). Ideally, this complex of potential problems is managed by an interactive team of specialists representing the disciplines of plastic surgery, dentistry, otolaryngology, speech pathology, audiology and social work, among others (Butow, 1984; Sadove et al., 2004). Important to the clinical management of CP patients is the choice of surgical protocol (timing, technique, etc.) for palatal reconstruction with consideration given to aesthetics, restoring “normal” growth trajectories, establishing velopharyngeal competency and, perhaps, resolving the underlying condition(s) that predisposes to OME (Nguyen and Sullivan, 1993; Parri et al., 2001; Summerlad, 2009).

Early studies of infants and young children with CP reported a very high prevalence of hearing loss, not affected by the usual methods for palate repair, but progressively lessened with aging throughout childhood and into adolescence (Graham, 1964; Smith, 1968; Moller, 1975; Webster and Eldis, 1978; Moller 1981; Fria et al., 1987). Others showed that the hearing loss was primarily conductive and directly attributable to the concurrent presence of a middle ear (ME) effusion in the absence of acute symptoms of infection (Bess et al., 1976; Smith et al., 1994; Flynn et al., 2009), a pathologic condition termed OME (Lokman et al., 1992). Indeed, screening studies and retrospective chart reviews documented a near universal prevalence of OME in CP infants and young children that, like the attendant hearing loss, decreased with advancing age (Stool and Randall, 1967; Smith, 1968; Paradise et al., 1969; Fara et al., 1973; Soudijn and Huffstadt, 1975; Moller, 1981; Robinson et al., 1992; Smith et al., 1994). Retrospective chart reviews and prospective studies reported no relationship between a child’s continued OME risk and the presence/absence of CL, CP laterality or CP type (Tuncbilek et al., 2003) and provided little to no evidence that the typical procedures for palatal repair or modifications in the stepped timing of those procedures resolved OME in the near-term (Watson et al., 1986; Dhillon, 1988; Robinson et al., 1992; Nunn et al., 1995). Other studies comparing palatoplasty methods with respect to lessening a child’s future OME risk (e.g. age 5 and older) reported inconsistent results made difficult to interpret because of their small per-group sample sizes, lack of appropriate controls (blinding, random assignment, etc.), use of surrogate outcomes to quantify OME persistence (e.g. number of VT insertions, hearing levels, etc.), or use of cross-sectional OME prevalence at a single time as the endpoint for evaluation (Butow et al., 1991; Spauwen et al., 1992; Hassan and Askar, 2007; Smith et al., 2008; Flores et al., 2010; Antonelli et al., 2011; Koudounakis et al., 2012; Carroll et al., 2013; Tiwari et al., 2013). Presently, there is no accepted clinical protocol to manage OME in CP and this remains an issue of active debate (Crysdale, 1976; Shaw et al., 2003; Phua et al., 2009; Ponduri et al., 2009; Klockars and Rautio, 2012).

To define best management practices for OME in CP children, there is a recognized need for well-controlled, prospective, preferably blinded studies that evaluate the comparative efficacy of specified interventions intended to decrease future OME risk (Sadove et al., 2004; Carroll et al., 2013). Prerequisite to designing such studies is the need for a better description of the “typical” time-course for OME risk in CP children. This is necessary to define the most appropriate outcome measure (e.g. presence/absence of OME at a specified age, OME “survival curves” across ages) and to estimate the sample size needed to detect between-group differences in the chosen outcome at a specified statistical power. Moreover, it is expected that as yet unidentified constitutive factors modify the time-course for OME risk in CP children. Appropriately designed clinical trials would include those factors as stratifying variables or would confine the enrolled population to those children with a moderate to high risk for continued OME expression. Past studies do not capture this information as they report simple OME prevalence by age, with OME diagnosis made using different methods with varying accuracies and largely ignore child-specific effects that impact future OME risk (Graham, 1964; Moller, 1975; Ovesen and Blegvad-Andersen, 1992; Robinson et al., 1992; Smith et al., 1994; Handzic-Cuk et al., 2001; Sheahan et al., 2002; Timmermans et al., 2006; Flynn et al., 2009; Szabo et al., 2010; Flynn et al., 2013). Here, we report the longitudinal time-course for OME expression in a cohort of similarly managed CP infants followed through 5 years of age.

METHODS

The data for this report were abstracted from those available for an ongoing, prospective, longitudinal study of craniofacial form, Eustachian tube (ET) function and ME status in CP children from presentation to the Cleft Palate Craniofacial Clinic at the Children’s Hospital of Pittsburgh of the UPMC (CPCC-UPMC, 3 months to 12 months of age) through age 6 years. There, the parent(s) of all non-syndromic infants with CP presenting to that clinic for long-term management of their child were informed of the study by a member of the study team who then explained the study design, parental obligations and study procedures to those expressing an interest. If agreeing to enroll their child, an informed consent form for study participation was reviewed and signed by the child’s parents and a member of the study staff. The full protocol was reviewed and approved by the University of Pittsburgh IRB. Eighty-two infants with non-syndromic CP (with/without CL) were enrolled.

Briefly, for this study, the standard assessment, treatment and management protocol for CP infants operational at CPCC-UPMC is supplemented by additional parent-child visits to the research clinics of the Division of Pediatric Otolaryngology, Department of Otolaryngology, University of Pittsburgh. These research clinic visits are scheduled pre- and post-palatoplasty, and then yearly through age 6 years. At each research clinic visit, an interval history is taken, an ENT exam is done, ME status is assessed by pneumatic otoscopy and tympanometry, and, beginning at 3 years of age, ET function is tested using standard manometric techniques if the tympanic membrane is not-intact (Casselbrant et al., 2014) or a pressure-chamber protocol if the tympanic membrane is intact (Swarts et al., 2014). Additionally, information related to craniofacial form is obtained from cephalometric x-rays done at 5–6 years of age on all enrolled children and on ET morphology from MRIs done at 4 and 6 years of age in a subset of the children. Information related to the timing and type of

all surgical procedures and the ME status and hearing assessments done at clinical CPCC-UPMC visits is collected by periodic reviews of patient records maintained by the CPCC-UPMC and ENT clinic at Children's Hospital.

For each assessment of ME status at the research clinic, the integrity of the right and left tympanic membranes is coded as intact or non-intact and, if non-intact, the presence/absence of a VT and its functionality, or of a perforation, and the presence/absence of otorrhea through the tube or perforation are recorded in the study chart. For ears with intact tympanic membranes, physician-diagnosed ME status is coded and recorded as acute otitis media, OME or "no disease". This information for all study visits and clinical examinations along with the ear-canal volume, tympanic membrane compliance and ME-ambient pressure-gradient recorded by tympanometry, if done, the results of any audiometric testing done at the CPCC-UPMC, and the dates and type of all surgical procedures are entered routinely into a computer file independently by two staff members. All paired records are compared periodically and identified discrepancies are reconciled by referral to the primary data source (e.g. study records, patient records). The reconciled database is then locked to retrospective change and used as the source file for all analyses.

For this report, the data for all enrolled children who achieved 5 years of age and had a study visit(s) at some time between their 5th and 6th birthdays were abstracted from that database and analyzed. There, the codes for ME status on sequential observations for each ear were examined by two investigators to identify the age in years (i.e. <1, 1, 2, 3, 4 and 5 years) at the first observation of ME status coded as "no disease" not followed by a ME assessment with an alternative status code (i.e. VT, perforation, otorrhea, acute otitis media, or OME). This was defined as the age at OME resolution (AOR). For ears that had not resolved their OME by or during the 5th year of life, the AOR was assigned a value of ">5 years". No AOR could be assigned to ears with one or more sequential "no disease" assignments followed by a VT insertion because of identified disease in the contralateral ear that was present for all assessments made during the 5th year of life. For all ears, the AORs recorded by the 2 investigators were compared and identified discrepancies reconciled by referral to the primary database.

To describe the temporal pattern for resolution of OME in this cohort, functions relating the cumulative frequencies of ears and persons to the AOR (for persons, the greater AOR for the right and left ears) were constructed and the parameters of best-fit curves to these functions were estimated using the method of least-squares. Also, each child was classified with respect to whether or not OME had resolved bilaterally before or during the 5th year of life. The effect of sex, race, Veau type and presence/absence of CL on the assignment to the OME-resolved and -unresolved subgroups was tested for significance using independent, continuity corrected Chi-square tests. Throughout, the format average $\pm$ standard deviation is used consistently.

RESULTS

Fifty-two (43 with CL) of the 82 enrolled CP children had at least 1 study visit between their 5th and 6th birthday, i.e. are older than 5 years of age. For these children, follow-up extended

through the ages of 5, 6, 7, 8 and 9 years in 10, 24, 7, 8 and 3 children, though the present analysis only considers the ME status through the 5th year of life.

In this subgroup, 29 children are males and the distribution of parent-assigned race for their child was 45 White, 2 Black, 3 Asian and 2 “mixed race”. Two, 11, 27 and 12 of the palatal clefts were classified as Veau 1 through 4, respectively. The average age at lip repair (n=43) was 0.51 ± 0.14 years and at palate repair was 1.13 ± 0.24 years, and all children had bilateral VTs inserted at the time of lip or palate repair as prescribed by the CPCC management protocol. Additionally, bilateral VTs were inserted if OME recurred in either ear after the previous VT became non-functional. Palate repair was done by one of six surgeons with a distribution of 31, 14, 3, 2, 2 and 1 cases/surgeon using the Furlow procedure alone (n=50) or a the procedure described as in the chart as a double opposing z-plasty (n=2). The average number of bilateral ME evaluations during follow-up in this cohort was 10.1 ± 3.1 (median=9, range=6–20) with all years represented for both ears of each child. Through age 5 years, 26, 13, 6, 4 and 3 children had 0, 1, 2, 3 and 4 bilateral VT reinsertions. One child (male, mixed race, Veau 4, Right and Left AOR = 2 and 5 years) had a revised palatoplasty at 1.9 years of age and 1 child (male, white, Veau 1, Right and Left AOR = 4 and 2 years) had a tonsillectomy at 3.5 years of age.

Prior to insertion of the first set of VTs, OME was not diagnosed in 1 ear of 3 children or in both ears of 2 children, but was diagnosed in all other ears (93%). Figure 1 shows the cumulative percent frequency of ears and children as a function of their AOR in years. Two children (4%) had no observations of OME in either ear at any time during follow-up. For the cohort, the cumulative percent of ears/children with OME resolution increased from 14.3/10.9% at age <1 year to 70.4/60.9% at age 5 years. Curve-fitting showed that the linear-equations, Percent Resolution (Ears) = $3.4 + 13.5 \times \text{Age}$, and Percent Resolution (Children) = $1.1 + 11.9 \times \text{Age}$, explained 99% of the variance in the distribution of those AORs ($r^2=0.99$, $p<0.01$ for both), documenting strict linearity.

By the endpoint for this analysis (through 5 years of age), 14 left and 14 right ears (18 children) had not and 35 left and 34 right ears (28 children) had resolved their OME. Resolution status could not be assigned for 3 left and 4 right ears (6 children) because of the presence of a patent VT for all observations during 5 years of age in combination with a pre-VT sequence of “no-disease” diagnoses. The right-left agreement with respect to OME resolution was 80%, i.e. 9 bilaterally unresolved, 28 bilaterally resolved, and 9 unilaterally resolved ($p<0.01$). On last testing, the distribution of tympanometric types for the 69 ears with OME resolution was 55 type A (78.7%, average pressure= -39 ± 40 daPa, average compliance= 0.6 ± 0.4 ml), 0 type B (0%) and 14 type C (20.3%, average pressure= -250 ± 65 daPa, average compliance= 0.8 ± 0.5 ml).

Table 1 cross-tabulates the frequency distribution of children for the OME-resolved and -unresolved subgroups by sex, race, Veau type and presence/absence of CL. None of those variables was a significant predictor of the child’s group assignment (all $p>0.05$).

Of interest, only a single episode of acute otitis media was diagnosed in 1 ear of 2 children during follow-up. In contrast, otorrhea through the VT or perforation was relatively frequent

(at least once in 40% of the children), occurring unilaterally in 12 children and bilaterally in 9 children, with repeat episodes in 4 ears. Past otorrhea was not predictive of subgroup assignment occurring in 33% and 39% in the unresolved and resolved subgroups, respectively ($p>0.05$).

DISCUSSION

OME, defined as an inflammation of the ME mucosa with varying amounts of accumulated fluid (i.e. effusion) within the normally air-filled ME cavity, is a relatively common presentation in infants and children (Bluestone and Klein, 2007). When extant, the ME fluid (i.e. effusion) dampens free movements of the tympanic membrane causing a conductive hearing loss that fluctuates in magnitude with changes in fluid volume, spatial distribution and other factors. Thus, there is not a 1:1 correspondence between extant OME and a detectable hearing loss, and the use of the latter to diagnose the former is neither specific nor sensitive. While the etiology of OME is believed to be multifactorial, an effect common to all is impairment of the Eustachian tube opening function (Bluestone, 2005), a pathophysiology known to precipitate a disease condition not different from OME (Casselbrant et al., 1985). Most OME episodes are of short duration, but, in a subset of children believed to be characterized by constitutively poor ET opening function, OME can persist for years. In those cases, no medical treatment effects disease resolution, but the probability of continued OME decreases with advancing age such that these children tend to “outgrow” their disease risk. The possibility of long-term hearing loss in children affected by persistent OME is typically managed by VT insertion which re-establishes ME pressure-regulation, promotes the clearance of ME fluid and restores near-normal hearing. However, that intervention is not without complications such as otorrhea through the tube and sequelae such as tympanic membrane scarring and thinning. Moreover, VTs are spontaneously extruded from the tympanic membrane over time with recurrence of persistent OME if the ET opening efficiency had not normalized during the interval (Bluestone and Klein, 2007).

The population of children with congenital CP is characterized by a near universal prevalence of OME in infancy and a much higher OME prevalence at all ages when compared to the respective populations of infants, children, adolescents and adults born without palatal clefts (Graham, 1964; Stool and Randall, 1967; Smith, 1968; Paradise et al., 1969; Moller, 1981; Flynn et al., 2009; Flynn et al., 2013). These data evidence an exceedingly high risk for persistent OME or, less likely, recurrent OME in CP infants that slowly decreases with advancing age. This risk is usually attributed to the abnormal morphology and spatial vectors for the ET and paratubal muscles characteristic of CP infants and children, an anatomy that imposes a constitutively poor ET opening efficiency (Doyle et al., 1986). If correct, the functional-anatomic deficiencies in the ET opening mechanism in CP children are not caused solely by the patent nasal-oral communication, as closure of the palatal defect using standard methods does not appreciably change OME risk (Watson et al., 1986; Dhillon, 1988; Robinson et al., 1992; Nunn et al., 1995). However, a degree of functional-anatomic normalization is achieved by adaptation and/or maturation during growth and development as reflected in the decreasing OME prevalence with aging in CP children (Moller, 1975; Robinson et al., 1992; Sheahan et al., 2002; Flynn et al., 2009; Szabo et al., 2010; Flynn et al., 2013).

For the population, an intrinsic variability in the degree of functional-anatomic deficiency across individual CP infants and children at any specified age is expected. This would be expressed as a variability across children in the OME risk at a given age. Importantly, the distribution of these risks within a population is an important parameter for estimating the group sample sizes required to achieve specified statistical powers for detecting “true” between-group differences in comparative studies of risk-modifying interventions. Also, the identification of individual characteristics that discriminate CP children with high and low future OME risks would prove useful in predicting future disease experience for a given child and may well define a set of candidate risk modifiers for targeted intervention.

The hypothesized variability in OME risk across CP infants cannot be tested using published data, as all past studies reported simple prevalence estimates for defined age groups irrespective of whether the design was a cross-sectional sampling across ages for a population or a longitudinal follow-up of individuals across ages within a population (Moller. 1975; Robinson et al., 1992; Sheahan et al., 2002; Flynn et al., 2009; Szabo et al., 2010; Flynn et al., 2013). These prevalence data are applicable only to populations and cannot be translated to individual risk assignments. Here, we analyzed longitudinal ME status data prospectively collected for a cohort of CP infants followed through 5 years of age to describe the distribution of the disease course for individual children. That analysis treated OME in CP children as a persistent (or recurrent) condition that resolves at different ages in different individuals reflecting the contribution of child-related factors to the variability in OME risk.

The results of that analysis documented the expected inter-child variability in continued OME risk as reflected in the wide distribution of resolution ages. The across-age distributions of ears and individuals with respect to continued OME risk was “flat” such that approximately equal numbers of ears or children in the cohort resolved their OME at age 2, 3, 4 and 5 years. This distribution “shape” largely discounts an effect of palatoplasty on near or future OME risk since the expected spike in frequency of children with OME resolution at 1 and 2 years of age, assuming such an effect, was not detected. The contribution of the child-related factors to the variability in continued OME risk is supported by the high left-right ear agreement in the OME resolution assignment at 5 years of age which strongly suggests that such factors couple the continued OME risks for the two ears of a child.

The distribution of resolution ages shown in the figure allows for estimation of the frequency of CP children with OME resolution at each age and the assignment of individual children to resolved/unresolved subgroups at any age. We suggest that the differences in the characteristics of individuals between the 2 subgroups defined at a specified age captures factors that directly impact OME risk. In a first exploration of this possibility, the effects of sex, race, presence/absence of CL, Veau type on subgroup assignment were tested, but none were significant predictors of disease resolution through 5 years of age. However, this study was not designed to test such hypotheses and the power to detect “true” differences for these comparisons was low. Nonetheless, with a larger sample size and the inclusion of other factors, this type of analysis promises to identify a set of risk-modifiers that can be targeted for intervention. Indeed, at the completion of follow-up on all children enrolled in the primary study, we plan to test the predictive value with respect to AOR of the measured ET

functional efficiency and structural dysmorphologies assessed at earlier ages. Also, the cumulative distribution of the frequencies of OME resolution by age can be recast as a “survival curve” for OME persistence over time. Such curves contain significantly more information than is represented in simple dichotomous subgroup assignments. Consequently, in designing clinical studies comparing interventions to lower OME risk in CP children, smaller sample sizes can be accommodated by taking advantage of this information and analyzing study results using statistical techniques for between-group comparisons of these “survival curves”.

The assignment of AORs based on longitudinal ME status data for individual ears and children assumes that the probability of OME during a given year is conditioned by the previous year’s ME status, and specifically that, for a given ear, a diagnosis of “no disease” significantly reduces the probability (i.e. risk) of an OME diagnosis at a later time for the same ear. This assumption is supported on examination of the temporal data for individual ears in this cohort where a no-disease assignment on any two sequential observations was followed by an OME diagnosis at any time in only 19 ears (18%), with 9 of those cases (47%) representing a single OME diagnosis embedded within a string of no-disease observations. To be conservative in assigning an AOR for individual ears, any OME observation was interpreted as evidence of continuously persistent OME to that age though it is more probable that short-duration OME episodes after a long string of “no disease” observations is caused by an etiologic factor such as an upper respiratory virus infection that transiently depresses ET opening efficiency and does not reflect a constitutive degree of inefficiency sufficient for disease presentation as persistent OME. To definitively answer this question, a greater sample density across all ages would be required and is recommended for incorporation into the design of future studies.

One limitation to this analysis is that AORs assigned at 5 years of age are presumably less reliable than those assigned at younger ages where the string of “no-disease” observations from that age through age 5 years strengthens confidence in the assignment. This possibility was examined using data for the complete period of follow-up available from the primary database. There, of the 14 ears with an AOR assigned at 5 years, 10 had follow-up data through greater ages with no OME diagnoses in those ears at the later times.

In summary, the risk for OME approaches 1 in cleft palate infants, is not affected by palatoplasty, but decreases with advancing age. There was a significant contribution of the individual to the observed variability in the AOR suggesting that factors characteristic of the individual impact continued disease risk. In this cohort, the temporal pattern of disease assignments was consistent with that expected for persistent, rather than, recurrent OME and diagnoses of acute OM were rare. All children had bilateral VTs inserted at the time of lip and/or palate repair and on observation of at least unilateral OME after the VT had become dysfunctional. As previously reported (Curtin et al., 2009), otorrhea through the tube was a common complication but this did not increase future disease risk. Overall, persistent OME had resolved in approximately 70% of the ears and 60% of the children by the child’s 6th birthday, but these rates need be referenced to populations where OME was managed similarly to that of the CPCC-UPMC as described in the Methods and Results sections.

Acknowledgments

Supported in part by: NIH grants DC007667 and DC011524

The authors thank Drs. Charles D. Bluestone, Margaretha L. Casselbrant, J. Douglas Swarts and Miriam S. Teixeira, and Ms. Kathy Tekeley, Jenna El Waaga and Julianne Banks for their assistance with recruitment, examinations and testings.

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Figure 1.
Cumulative frequency of ears (open circles) and children (closed squares) as a function of the age at OME resolution.

TABLE 1

Cross-tabulation of the number of children in the OME-resolved and OME-unresolved subgroups by sex, race, Veau type and presence/absence of CL and the chi-square value, degrees of freedom (DF) and probability level (P-value) for the effect of each variable on subgroup assignment.

Variable	Grouping*	Number Resolved	Number UnResolved	Percent Resolved	Chi-Square	DF	P-value
Total		28	18	61			
Sex	male	18	7	72	2.85	1	0.09
	female	10	11	48			
Race	white	22	17	56	2.14	1	0.14
	black	2	0	100			
	Asian	2	1	67			
	other	2	0	100			
Veau	Veau 1	2	0	100	4.22	2	0.12
	Veau 2	8	2	80			
	Veau 3	11	12	48			
	Veau 4	7	4	64			
Cleft Lip	+	21	15	58	0.44	1	0.5
	-	7	3	70			

* Collapsed groups (lettered) for statistical comparisons so as to satisfy the recommended minimum cell size for Chi-square analysis.