From the Department of Clinical Science, Intervention and Technology, Division of Ear, Nose and Throat Diseases

HEARING IN CHILDREN WITH CLEFT PALATE

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Hearing in children with cleft palate

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To All Children with cleft palate

ABSTRACT

Objective: The overall aim of this thesis was to collect longitudinal information about hearing thresholds and complications due to otitis media with effusion (OME) in children with cleft palate. Since OME is highly prevalent in children with cleft palate, many authors have hypothesized that the hearing loss associated to OME contributes to the delayed development of early speech and language often seen in these children. There is a lack of knowledge whether the OME-associated hearing loss is more severe in children with cleft palate compared to children with OME but without cleft.

Methods: Audiological and otological data were reviewed retrospectively in a group of children with unilateral cleft lip and palate (UCLP) from 4-10 years of age. Results of hearing tests and the number of ventilation tube (VT) treatments were analyzed (study I). In the prospective longitudinal group comparison study audiological and otological data were collected in one group of children with cleft palate, and another group of children with OME but without cleft palate. The children were followed from the neonatal auditory brainstem response assessment (ABR) at 1-4 months of age to 36 months of age. At seven different test occasions, age-appropriate hearing tests were performed (study II).

Results: In the group of children with UCLP, the proportion of children with hearing loss in the speech frequencies decreased with age. However, when examining the higher frequencies, this improvement was not found. There were no significant correlations between the number of VT treatments and hearing thresholds at 7-10 years of age. Four children (12%) presented with complications; perforation of the ear drum, requiring surgery (two children) and acquired cholesteatoma (two children). In the prospective longitudinal study, the comparison of the median four frequency average at 500, 1000, 2000 and 4000 Hz (4FA), and the median thresholds at 500 and 4000 Hz, at 12 months of age, demonstrated significantly better levels in the group of children with cleft palate, which might be explained by the early VT treatment at the time of the palate repair, often at 6 months of age ($p < 0.001$). There were no significant group-wise differences in the median 4FA or in any discrete frequencies at 24 and 36 months of age. Both groups improved over time from the neonatal ABR-test to the test at 36 months of age, $p < 0.05$ in CP±L-group; $p < 0.001$ in group without CP±L. When analyzing the thresholds from 12 months to 36 months of age, there was a significant improvement in the group without CP±L ($p < 0.001$), but not in the group with CP±L. At 36 months of age the median 4FA was normal in both groups.

Conclusion: Children with cleft palate have a high prevalence of OME, with a subsequent risk for long-term hearing loss. The early VT treatment in children with cleft palate appears to be favourable for the short-term hearing; however, this should be weighed against the risk for complications. Therefore, this group of children requires close monitoring with otological examinations and audiological assessments to ensure that the common OME-associated conductive hearing impairment is managed appropriately.

LIST OF SCIENTIFIC PAPERS

I. Tengroth, B., Hederstierna, C., Neovius, E., & Flynn, T. (2017). Hearing thresholds and ventilation tube treatment in children with unilateral cleft lip and palate. Int J Pediatr Otorhinolaryngol, 97, 102-108. doi:10.1016/j.ijporl.2017.03.031

II. Tengroth, B., Lohmander, A., & Hederstierna, C. (2019). Hearing Thresholds in Young Children With Otitis Media With Effusion With and Without Cleft Palate. Cleft Palate Craniofac J, 1055665619889744. doi:10.1177/1055665619889744

CONTENTS

LIST OF ABBREVIATIONS

ABR	Auditory brainstem response
CP±L	Cleft palate with or without cleft lip
dB HL	Decibel Hearing Level
dB nHL	Decibel normalized Hearing Level
ET	Eustachian tube
4FA	Average of the thresholds at 500, 1000, 2000 and 4000 Hz
ICP	Isolated cleft palate
OME	Otitis media with effusion
PTA4	Pure Tone Average based on four frequencies, 500, 1000, 2000 and 4000 Hz
PTAHF	Pure Tone Average High Frequencies, based on 6000 and 8000 Hz
UCLP	Unilateral cleft lip and palate
VRA	Visually reinforced audiometry
VT	Ventilation tube

INTRODUCTION

Children born with cleft palate need health care from a wide range of professions. Feeding, speech, dentition and hearing can be affected, and the interventions should be supported by a strongly evidence-based knowledge. If hearing impairment caused by otitis media is a risk factor for delayed speech and language development and later problem with academic achievement in children with cleft palate, has been discussed but not yet clarified. (Eshghi et al., 2019; Schonweiler et al., 1999; Shaffer et al., 2017). However, extended knowledge on hearing loss related to otitis media with effusion (OME) in children with cleft palate is needed before its relationship with speech and language development can be further explored.

1 BACKGROUND

1.1 Epidemiology cleft palate

Cleft palate with or without cleft lip (CP±L) is one of the most common birth anomalies, and the incidence is approximately 1-2 per 1000 births with ethnic and geographic variations (Hagberg et al., 1998; Mastroiacovo et al., 2011; Mossey et al., 2009; Mossey and Modell, 2012; Tanaka et al., 2013). Studies of the prevalence of additional malformations or syndromes exhibit different results, but the definition of associated anomalies and syndromes varies (Milerad et al., 1997; Mossey and Modell, 2012). Chetpakdeechit (Chetpakdeechit et al., 2010) found that in a group of 343 Caucasian children with isolated cleft palate (ICP), other birth defects existed in 34 % of the children, and the risk was 1,7 times higher for a total compared to a partial ICP. Moreover, ICP has been shown to have a higher prevalence of associated malformations than unilateral cleft lip and palate (UCLP) (Pereira et al., 2018).

1.2 Embryology and etiology

The central development of the face, head and neck occurs during the first 8 weeks of embryogenesis, and during this period most developmental abnormalities occur.

The intermaxillary segment, which derives from the first pharyngeal arch gives rise to the philtrum of the upper lip and the primary palate. The upper lip formation is completed in the sixth or seventh week. The remainder of the palate forms from the palatal shelves which appear late in the sixth week. As the palatal shelves proliferate, they start to fuse, from anterior to posterior. The fusion of the hard palate is complete in the tenth week. The soft palate and uvula develop from mesenchymal proliferation at the posterior aspect of the hard palate (Coleman and Sykes, 2001).

The etiology of cleft palate is multifactorial and most of the cases are believed to be caused by an interaction of various genetic and environmental factors. Risk factors as folic acid deficiency during pregnancy has been discussed (Millacura et al., 2017). An increased risk for cleft palate is also seen due to medication with anticonvulsive drugs such as valproate during pregnancy, and smoking and alcohol consumption during pregnancy. (Centers for Disease Control and Prevention)

1.3 Classification of cleft palate

The primary palate includes the portion of the maxilla anterior to the incisive foramen (pre-maxilla), and the secondary palate involves the palatal shelves posterior to the incisive foramen. The secondary palate is divided into the hard and soft palate.

The subjects with cleft palate in the present two studies had either a unilateral cleft lip and palate (UCLP), or an isolated cleft palate (ICP). ICP can involve the soft palate only or the soft palate combined with different degrees of cleft of the hard palate.

A) B)

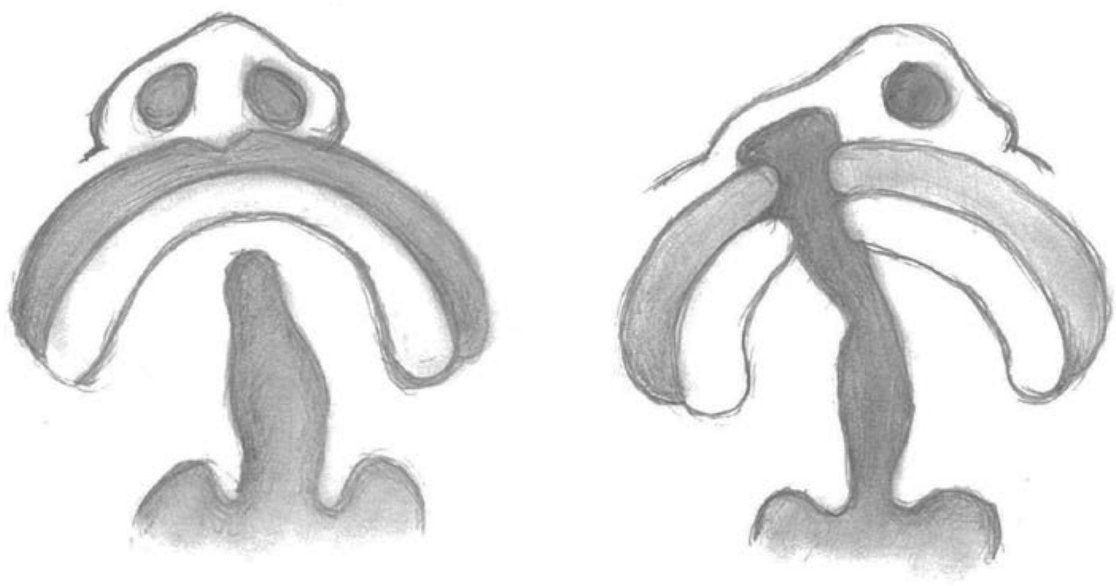


Fig 1. A Isolated cleft palate (ICP), B Unilateral cleft lip and palate (UCLP) *Illustration by Liisi Raud Westberg*

2 OTITIS MEDIA WITH EFFUSION

2.1 Prevalence and etiology of OME

Bluestone and colleagues examined the role of the Eustachian tube (ET) in the pathogenesis of otitis media (Bluestone, 1996). Other authors have suggested that the dysfunction of the ET is caused by infections in the middle ear.

Children with cleft palate with or without cleft lip (CP±L) have been displayed to have a high prevalence of otitis media with effusion (OME) in a number of studies (Y. W. Chen et al., 2012; Flynn et al., 2009; Grant et al., 1988; Klockars and Rautio, 2012; Kwan et al., 2011; Valtonen et al., 2005; Yang et al., 2012). In children with cleft palate, the dysfunction of the ET is due to abnormalities in the morphology and/or the abnormal insertion of the palatal muscles, m. tensor veli palatine and the m. levator veli palatine (Matsune et al., 1991). The lateralization of the insertion of the muscles causes a lack of anchorage, which does not allow proper opening of the Eustachian tube, and inability to equalize the pressure in the middle ear with the following risk for retraction of the tympanic membrane and secretion of mucus. Some authors suggest that the dysfunction may be related to a dilated tube (Tasaka et al., 1990; Todd, 1983).

Fig 2. The horizontal position of the Eustachian tube in children. *Illustration by Liisi Raud Westberg*

The etiology of OME in general population is multifactorial and different risk factors increase the prevalence rate. Age, exposure to tobacco smoke, respiratory infection, lack of breast-feeding in infancy, craniofacial abnormalities, adenoid hypertrophy and family history of otitis media has been identified as risk factors (Daly et al., 2010; Martines et al., 2011).

In general pediatric populations the prevalence rate of OME is decreasing with age but several authors describe that there are two peaks in prevalence, one before 2 years of age and a smaller peak at 5 to 7 years of age (C. H. Chen et al., 2003; Sade et al., 2003; Tos et al., 1983; Zielhuis et al., 1990) However, in children with cleft palate malformations the high prevalence of OME is not improved as much as in the general population and the problem may continue throughout childhood until adult age (Alper et al., 2016; Flynn et al., 2013; Flynn et al., 2009; Handzic-Cuk et al., 2001; Sheahan et al., 2003; Smith et al., 1994).

2.2 OME and hearing loss

The hearing loss associated with OME is fluctuating in degree due to the variable amount and viscosity of the fluid in the middle ears at each episode. Hearing sensitivity as a function of OME has been examined in a prospective study of children from 5 to 36 months of age by Gravel et al. Hearing thresholds were assessed bimonthly and an average threshold of the test frequencies for each visit was then averaged across all visits in each year. The children who were classified as bilaterally OME positive during year 1, 2 and 3 had significantly poorer hearing thresholds than children who were classified as OME free. Furthermore, the analysis showed that, as a group, there was no long-term effect of OME on the average thresholds of the four-frequency range when the middle-ear became OME free (Gravel and Wallace, 2000). In a systematic and descriptive review, the effect of OME on children's listening abilities were analyzed. In nine studies, the pure tone average thresholds (3PTA at 500, 1000 and 2000 Hz) were in the range of 18-35 dB, and in these studies the age of the children ranged from 2 to 16 years of age. The audiometric configuration was typically flat with the most prominent hearing loss in the lower frequencies, 250 and 500 Hz and at 8000 Hz when this frequency was tested. In this review the authors pointed out that both speech-in-quiet and speech-in-noise assessments were found to be impaired but there is a need for standardized speech test material to be able to evaluate hearing related disabilities (Cai and McPherson, 2017).

Some studies suggest that the hearing loss in children with cleft palate and OME is more pronounced than in children with OME but without cleft palate. (Broen et al., 1996; Flynn et al., 2009). In a study by Flynn et al., two groups of children, one group with UCLP and one group without cleft were followed prospectively, from 1 to 5 years of age. The hearing loss in ears with OME in children with cleft palate was significantly more pronounced compared to the hearing loss in ears with OME in children without cleft. Hearing impairment in the higher frequencies has been demonstrated in children with chronic otitis (Gravel et al., 2006; Hunter et al., 1996; Margolis et al., 2000; Ryding et al., 2005) and in children with cleft palate (Flynn et al., 2013; McDermott et al., 1986). Mc Dermott and colleagues examined the hearing thresholds and compared the thresholds in children with cleft palate, children with a high incidence of middle-ear disease but without any craniofacial anomalies and a control group of children with low incidence of middle-ear disease. The high-frequency thresholds, 8000-20000 Hz were statistically different in the two groups with a high incidence of middle-ear disease compared to the control group. Moreover, there was no statistical difference between the group with cleft palate and the group of children with a high incidence of middle-ear disease but without any craniofacial anomalies. A toxic effect and a lack of oxygen supply has been suggested to be the reason for this hearing loss (Kobayashi et al., 1988).

2.3 Tympanic membrane pathology

Many studies have reported about the frequencies of complications and sequelae of the tympanic membrane in children with persistent OME (Daly et al., 2003). Myringosclerosis and segmental atrophy are very common in ears treated with ventilation tubes, but several studies have not revealed any significant hearing loss due to these abnormalities (Johnston et al., 2004; Schilder et al., 1997; Tos and Stangerup, 1989).

2.4 Treatment with ventilation tubes and risk for following complications

Treatment with ventilation tubes (VT) are very common in children with CP±L, often at the time of the palatal repair. The optimal time for VT insertion and the risk for complications as otorrhea, myringosclerosis, retraction, perforation and granulation of the tympanic membrane, permanent hearing impairment, and post-VT insertion cholesteatoma has been discussed in many studies (Imbery et al., 2017; Karanth and Whittemore, 2018; Klockars and Rautio, 2012; Phua et al., 2009; Ponduri et al., 2009; Shaffer et al., 2018). In a systematic review by Kuo and colleagues, post-VT complications and sequelae are described in seven articles. Eardrum perforation occurred in 1.3 to 19% of ears treated with VT during 1 to 9 years of follow-up. However, the included studies were underpowered cohort studies, and comparison of VT treated children and non-VT treated regarding outcome of each complication was insufficient because of very-low-strength evidence. The author concluded that "studies up to date does not provide sufficient evidence on which to base the clinical practice of how to treat OME-related hearing loss in children with cleft palate" (Kuo et al., 2014).

Felton et al. (2018) reviewed six studies to examine the effectiveness and complications of ventilation tube placement before palatal repair. Three of the included studies reported 94-97% of infants with cleft palate having OME at 3-6 months of age. The authors of this review study concluded that early VT insertion in children with CP±L enables normal hearing thresholds in children with CP±L at an early age. On the other hand, there was no comparison regarding long-term outcomes between children with VT prior to palatal repair versus VT post palatal repair.

2.5 Impact of OME on speech and language development

The hearing loss associated with otitis media has been proposed to have a negative impact on early language acquisition. In a prospective cross-sectional study, Friel-Patti and Finitzo examined a group of children from 6 to 24 months of age regarding the prevalence of OME related to hearing over time. The receptive and expressive language skills were evaluated at 12, 18 and 24 months of age, and showed that language skills were significantly negative correlated with the number of days with effusion and hearing over time (Friel-Patti and Finitzo, 1990; Shriberg et al., 2000). On the other hand, several prospective and randomized clinical trials suggest none to minor negative correlation of OME to children´s later speech and language development in otherwise healthy children (Paradise et al., 2005; Paradise et al., 2003; Zumach et al., 2010). Roberts et al. (2004) performed 11 meta-analysis of prospective studies and found no to very small negative associations of OME and associated hearing loss to children's speech and language development.

Associations between OME associated hearing loss early in life and perceiving speech in noise and tasks that require equal binaural hearing at school age were examined in a prospective study by Schilder and colleagues. A group of children classified as "very persistent OME" group at pre-school age scored significantly lower on the speech-in-noise test compared to a group of children with a completely negative OME history (Schilder et al., 1994). In a prospective study by Gravel and colleagues on children with OME in the first 3 years of life, the assessments with conventional audiometry and extended high-frequency audiometry, distortion product otoacoustic emissions, acoustic middle ear muscle reflexes, auditory brain stem response (ABR), and higher-order auditory processing measures such as masking level difference and speech-in-noise were performed at a mean age of 8 years. Hearing loss in the extended high frequencies 12.5 and 14 kHz, the contralateral acoustic middle ear muscle reflex and the latency of the Wave V ABR response were significantly associated with early hearing loss and OME. There was no significant relation between distortion product OAE and early hearing loss and OME, indicating normal middle ear function. Psychoacoustic and speech-in-noise measures were not associated with early OME and hearing loss (Gravel et al., 2006).

For typically developing children, OME-related hearing loss might not be a substantial risk factor for later speech and language problems or academic achievement. However, since most of the studies analyzed the prevalence of OME rather than hearing loss, there is a lack of knowledge of the OME-associated hearing loss. Consequently, the question whether the hearing loss due to OME in early childhood is more severe in children with CP±L compared to children with OME but without cleft, and therefore might be a risk factor for later speech and language problems, is still to be answered (Hubbard et al., 1985; Eshghi et al., 2019; Schonweiler et al., 1999). In particular there is a lack of longitudinal studies on hearing thresholds in young children with CP±L, and in comparison, with children with OME but without cleft palate. Such knowledge could guide in choice of intervention as well as be a basis for future investigations if OME-related hearing loss is a risk factor for speech and language problems.

A summary of four studies conducted to compare hearing thresholds in children with and without CP±L, and two studies comparing audiological and early speech outcome in children with cleft palate with early VT treatment versus late treatment is presented in table 1.

Table 1. Summary of four studies conducted to compare hearing thresholds in young children with and without CP±L, and two studies (Hubbard and Schönweiler) comparing audiological and early speech outcome in children with CP±L, with early VT treatment versus late VT treatment.

First Author Year	Design	No. of children	Cleft type	Age	Hearing sensitivity	Recruitment of group without cleft/control group	Data collection	Results	Comments
Broen 1996	prospective longitudinal 2 groups	57	CP± L non-syndr	9-30 months	Screening 20-30 dB VRA in soundfield 500, 1, 2 kHz	Children without cleft: Lists of parents who expressed an interest to participate	3 months interval	Children with cleft failed the HS more often at almost every age. Some cleft children who failed tymp in only one ear failed HS in FF at 9 and 12 m. Early VT associated with better HT	
Valtonen 2005	Controlled prospective	72	CP± L non-syndr	6 months-6.5 years	3PTA/ear, at end of follow-up	33 children with OME but no cleft palate All children had VT before 7 months of age, except one in control group	At end of 6 years of follow-up 3PTA for both air and bone conduction	No significant differences in hearing levels between the groups. HL associated with perforation or retractions	No information about hearing thresholds before end of follow-up
Flynn 2009	prospective longitudinal 2 groups	42	UCLP non-syndr	1-5 years	3-4PTA	Children without cleft: All babies born 2001, invited with the same inclusion criteria	1, 1.5, 3, 5 years	Ears with OME had more pronounced hearing loss in cleft group	Group with UCLP were assessed with a lower age-appropriate level of test method at 1, 1.5 and 3 years of age, compared to control group
Eshghi 2019	prospective longitudinal 3 groups	94	CP± L non-syndr	12-24 months	pure tone audiogram at 12 and 24 months	40 children in CP± L-group, 29 children with OM, OM=Otitis media TD=Typically developed 25 TD children. Recruited from an ongoing multisite long study on language development	tymp at 12, 14, 18 and 24 months audiogram at 12 and 24 months	Cleft group had slower expressive vocabulary growth than TD group. At 12 m 71/77 children had normal hearing-no sign diff between groups. All OM children had tubes	Regression analysis: Type of tympanogram and mean hearing level were observed to predict vocabulary growth from 18 to 24 months of age, but no strong relationship

Hubbard 1985	cross sectional 2 groups	48	CP± L non-syndr	3 months-11years	3-PTA Consonant articulation	24 closely matched pairs of children with cleft palate, one group had VT at a mean age of 3 months,the other group at 30.8 months	5-11 years	Hearing thresholds and consonant articulation were less impaired in the group with early VT insertion	Routine use of antimi-crobials in the group with early insertion
Schönweiler 1999	retrospective	370	CP± L non-syndr	4.5 years	3-4PTA, at follow-up	Group 2: fluctuating uni or bilat conduc-tive HI 20 -40 dB Group 1: constant normal hearing	Speech and language outcome at 4-5 years was evaluated	Children with conduc-tive hearing loss had significantly less favour-able development of speech and language	The rate of VT treatment is not documented and the follow-up routines were different for the children Palatoplasty and veloplasty per-formed at 18-24 months of age

3 AIM

3.1 General aim

The overall aim of this work was to assemble longitudinal information about hearing thresholds and complications due to OME in children with CP±L.

3.2 Specific aims

The study specific aims were in

Study I to:

- Define the hearing thresholds of a group of children with UCLP from 4 to 10 years of age and try to elucidate alterations of the hearing thresholds with increasing age.
- Describe the prevalence of perforation and acquired cholesteatoma and verify if VT treatments increase the risk for permanent hearing loss and acquired cholesteatoma in this study group.

Study II to:

- Examine if the OME-related hearing loss in early childhood in children with CP±L is more severe compared to children with OME but without cleft palate.
- Examine if the air conduction thresholds improve with age in children with CP±L.

4 SUBJECTS AND METHODS

4.1 Study groups

4.1.1 Study I

Thirty-seven children (28 boys and 9 girls) born between 1998 and 2006 with UCLP without additional malformations and/or syndromes, were enrolled in this retrospective medical chart review. The children were participants in a multicentre randomized trial on palatal surgery, the Scandcleft project (Semb et al., 2017) in which all children were randomized to either a one-stage or a two-stage palatal repair.

All children in the present paper were treated by the Stockholm Craniofacial Team, Karolinska University Hospital. Two children had incomplete audiometric data, two children moved from the area which resulted in 33 children (25 boys and 8 girls) included in the study.

Ethical approval was obtained by the regional ethical committee for the Scandcleft project (Dno. 97-372).

4.1.2 Study II

Two groups of children were followed prospectively and longitudinally from 9 months of age until 36 months of age. Sixteen children with CP±L and 18 children without cleft but with OME were initially enrolled in the study.

All babies with isolated cleft palate born in the Stockholm region between 2012-2014 without any associated anomalies, syndromes or other physical impairment and at least one native Swedish speaking parent, were invited to participate in this study. The recruitment was originally connected to the international project Timing of primary surgery of cleft palate (TOPS) (Shaw et al., 2019). However, during the second half of the recruitment period, babies born with unilateral cleft lip and palate fulfilling the same inclusion criteria, were also invited to participate, in order to expand on the number of individuals in the cleft group. All the children in the cleft group were treated by the Stockholm Craniofacial Team, Karolinska University Hospital.

The infants in the group without cleft palate but with OME were recruited from the group of children who failed the neonatal primary hearing screening test and had been referred to the Hearing Department at Karolinska University Hospital for assessment with an ABR test. The children with ABR thresholds higher than 30 dB nHL in at least one ear, were invited to the study. Examination with otoscopy, tympanometry, and ABR was performed to be able to exclude children with sensorineural hearing impairment. If the child at the next appointment at 6-9 months of age had

OME in at least one ear, they were offered to be enrolled in the study. The inclusion criteria, apart from having a cleft palate, were the same as for the cleft group. Three children without cleft palate were later excluded from the study because of a permanent unilateral conductive hearing impairment (one child), and a mild bilateral sensorineural hearing impairment (two children). The remaining group of 31 age-matched children consisted of 16 children with CP±L (10 males), and one group of 15 children with OME (9 males) but without CP±L.

All children in the CP±L-group were treated with ventilation tubes bilaterally, at the time of the soft palate repair. Twelve children with isolated cleft palate received a complete palatal surgery at a mean age of 8.0 months (SD 2.9). The four children with unilateral cleft lip and palate had a soft palate repair at a mean age of 6.2 months (SD 0.3) and a hard palate closure at 24 months of age. The children in the group without CP±L were treated with ventilation tubes in accordance with current evidence for children with OME (Hellström et al., 2011). None of the children in the group without cleft palate had ventilation tubes in place before 13 months of age.

Ethical approval was obtained by the regional ethical committee for the main study: Early development of hearing, speech and language in infants born with cleft palate and infants with early ear problems (2012/46-31/2).

4.2 Methods

4.2.1 Medical records (Study I)

The audiograms, the number of hearing tests and the number of VT treatments were reviewed from when the children were 4 years until 10 years of age. The data were split in two age groups, 4-7 years and >7-10 years of age.

4.2.2 Otoscopy (Study II)

In study II otoscopy was performed at each appointment by one of the authors (BT) and was classified as normal, abnormal or with tubes in situ. OME was diagnosed if at least one of the following conditions was met: abnormal flat tympanometry (type B); abnormal otoscopy with signs of fluid in the middle ear; or abnormal tympanometry (type C) and abnormal otoscopy with signs of fluid in the middle ear.

4.2.3 Acoustic impedance (Study II)

The middle ear has an important role to compensate for the impedance mismatch between the air in the outer ear canal and the fluid in the inner ear. Assessments of the acoustic impedance provide information about the effectiveness of the mechanical system in the middle ear, and the resistance in the ear against sound energy flow, i.e. the efficiency of the sound transmission system in the middle ear. Admittance is the reciprocal of impedance and represents the ease of the sound energy flow through the system.

Tympanometry is a technique for measurement of impedance. A probe delivers a pure tone in the external ear canal, and a pump connected to the probe alters the air pressure in the canal from +200 daPa above (positive pressure) to -400 daPa below (negative pressure) atmospheric pressure. With a carrier frequency of 226 Hz, the stiffness of the tympanic membrane and the ossicular chain, and the air pressure in the external canal and the middle ear are the main contributors to the impedance. The compliance is the reciprocal of stiffness and can be defined as the quotient of a change in volume and the required change in pressure to achieve this volume change. At 226 Hz the compliance for an air-filled cavity of 1 ml is 1 mmho and the compliance can be expressed in equivalent volume in ml or cm^3. The tympanic membrane is most mobile when the air-pressure in the external ear canal reaches the pressure in the middle ear. The normal middle ear pressure in children varies between +50 daPa above to – 100 daPa below atmospheric pressure.

Tympanometry was completed with standard equipment, and was classified as normal (type A), flat tympanogram (type B), negative pressure (type C) or with tubes in situ (Liden, 1969).

4.2.4 Auditory brainstem responses (Study II)

Auditory brainstem responses (ABR) were registered using an Interacoustics Eclipse system EP 25. The stimulus consisted of a click (100µs) with a repetition rate of 39.1 per second. Each recording was individually analyzed by the audiologist and one of the authors (BT).

ABR thresholds of 30 dB nHL or better were classified as “pass”, thresholds > 30 dB nHL as “fail” in the group-wise comparison at 1-4 months of age.

4.2.5 Hearing sensitivity (Study I and II)

Pure-tones or warble-tones were used with audiometers according to the international standard IEC 60645 and calibrated according to ISO 389.

For study I conditioned play audiometry or tone audiometry under TDH-39P (Telephonics) headphones was applied to obtain ear specific thresholds for 500, 1000, 2000, 4000, 6000 and 8000 Hz. A four frequency pure-tone average (PTA4) of 500, 1000, 2000 and 4000 Hz and a high frequency pure-tone average (PTAHF) based on 6000 and 8000 Hz were calculated for each ear. For each child, the audiograms with the best thresholds when they were 4-7 and > 7-10 years of age were chosen for the analysis. Hearing screening according to clinical protocol at 10, 15 and 20 dB HL was performed at the age of 4-7 years in seventeen children. The screening threshold is not necessarily the absolute threshold, and a comparison of mean or median PTA4 does not depict the true situation. Therefore, we chose to compare the proportion of children with a normal PTA4 and the children with hearing loss at the two different age spans.

The classification of grades of hearing impairment by HEAR (Martini, 2001) are demonstrated in table 2.

Table 2. Classification of hearing impairment by the better ear.

PTA4 in better ear	
Normal	≤20 dB HL
Mild	>20-40 dB HL
Moderate	>40-70 dB HL
Severe	>70 dB HL

The number of children with audiological data in the two age groups 4-7 and > 7-10 years are presented in table 3.

Table 3. Number of children with data in the two age groups 4-7 and > 7-10 years. The number of children with data at both occasions are presented within parentheses.

	Number of children	
Group	**4-7 y**	**7-10 y**
PTA4	33(30)	30
PTAHF	21(17)	28(17)

At 4-7 years of age, 12 children had missing data at 8000 Hz, and for one of those 12 children there is also missing data at 6000 Hz bilaterally and for one child unilaterally.

In study II the children were followed by assessment of hearing sensitivity at 8 test occasions from the neonatal ABR test at 1-4 months of age until 3 years of age. At the ages of 9, 12, 15, 18, 24, 30 and 36 months of age (±4weeks) data about hearing thresholds were collected and at the same appointment the middle ear status was examined.

Behavioral, visually reinforced audiometry (VRA) and/or conditioned play audiometry was performed to attain frequency-specific thresholds. An experienced pediatric audiologist decided which test-method to use, taking into consideration the child´s ability to comply with the assessment. In the VRA-test, a picture appears on a screen when the child responds appropriately to a stimulus. In the young infants the tests often had to be done in sound-field, but from 30 and 36 months of age most of the children accepted headphones. A screening level of 20 dB HL was used when the air-conduction thresholds at 500, 1000, 2000 and 4000 Hz were assessed and an average of the thresholds at those frequencies (4FA) was calculated. The better ear was determined to be the ear with the best 4FA, and if the result was the same in both ears, the right ear was chosen. For all the analyses in study II the better ear was chosen since ear-specific thresholds are not always obtained when the test is performed in a sound-field.

In order to be able to assess as many subjects as possible longitudinally, three ages were chosen, 12, 24 and 36 months of age. Due to missed appointments and noncompliance, it was not possible to compile data for this longitudinal analysis on all children in the study. Twenty-five children were possible to assess longitudinally; 13 children with CP±L and 12 without cleft. Sixteen of these 25 children had complete data at the planned occasions and in 9 children the results from the visit directly prior to or after that age, were chosen for the analyses. Group-wise comparisons of median ABR thresholds at 1-4 months, median 4FA and frequency-specific median thresholds at 12, 24 and 36 months of age, were included in this longitudinal analysis.

To be able to compare the proportion of children with hearing loss at each age, 9 to 36 months, the results of the 4FA in the better ear were classified as "pass" or "fail". It was not possible to determine the 4FA in some children because of non-compliance and missing data. The children with results at less than four frequencies were included if the average of those frequencies could only yield a "fail" result, otherwise the subject was excluded in the comparison at this age. If the 4FA was better than the selected cut-off level at 26 dB HL, the result was classified as "pass ". From 24 months of age an additional cut-off level at 21 dB HL was also implemented since the ability to cooperate in the assessment situation generally increases at this age.

4.3 Statistical methods and calculations (Study I and II)

Non-parametric tests were performed when comparing hearing thresholds due to their non-normal distribution.

4.3.1 (Study I)

The McNemar´s test (Statistica, Version 10) was performed to examine the change in proportion of children with hearing loss in the two age groups. The relation between the number of VT-treatments before 10 years of age and the hearing thresholds was examined with the Pearson Correlation test (SPSS, Version 22).

4.3.2 (Study II)

The Mann-Whitney U test was performed to examine the group wise differences in ABR, in 4FA and in hearing thresholds at discrete frequencies. Friedman ANOVA was used to analyze if the hearing thresholds improved over time. Statistica 13.2 (Stat Soft®).

The difference in proportion of pass and fail between the CP±L-group and the group without cleft palate was analyzed with performance of the Fisher´s exact two-tailed test due to the small sample sizes.

5 RESULTS

5.1 Study I

5.1.1 Audiometry

According to clinical protocol a screening method was used at the assessments at 4-7 years of age in seventeen children. The screening level was 10, 15, or 20 dB HL.

Regarding the PTA4 at 4-7 years of age, two children had a bilateral mild hearing impairment, and five children had a unilateral mild hearing impairment. One child had a unilateral moderate hearing impairment. At > 7-10 years of age none of the children had a bilateral hearing loss in the PTA4, but four children had a mild unilateral hearing impairment. Three children had missing data, but no hearing impairment at 4-7 years of age. Thirty children with complete audiometric results from 500-4000 Hz at both age intervals were included in the analysis of the difference in proportion of children with PTA 4 > 20 dB HL (McNemar´s test). A significant decrease was found in the proportion of children with PTA 4 > 20 dB HL between the two age groups ($p < 0.001$).

Examining PTAHF at 4-7 years, revealed three children with a mild bilateral, one with a moderate bilateral, four with a mild unilateral and one with a moderate unilateral hearing impairment. In the older age group > 7-10 years, four children had a bilateral mild hearing impairment and one child a moderate bilateral hearing impairment. Two children had a mild unilateral and one a moderate unilateral hearing impairment. At this age two children had missing data at 8000 Hz but exhibited thresholds at 15 dB HL at 6000 Hz. The statistical analysis of the seventeen children with complete audiometric data in the higher frequencies at both age intervals, revealed no significant difference in proportion of children with hearing impairment in the higher frequencies between the two age groups.

Table 4. Number and percent of children with unilateral and bilateral hearing loss grouped by age and degree of hearing loss. Unilat: unilateral hearing loss, bilat: bilateral hearing loss.

Group	PTA4	unilat	bilat	Group	PTAHF	unilat	bilat
4-7 y	>20-40	5(15%)	2(6%)	4-7 y	>20-40	4(19%)	3(14%)
(n=33)	>40-70	1(3%)	0	(n=21)	>40-70	1(5%)	1(5%)
7-10 y	>20-40	4(13%)	0	7-10 y	>20-40	2(7%)	4(14%)
(n=30)	>40-70	0	0	(n=28)	>40-70	1(4%)	1(4%)

5.1.2 Prevalence of complications due to VT treatments

Twenty-nine children were treated with ventilation tubes, two as early as before six months of age, and most children had their first VT placement between 6 and 24 months. The number of VT treatments up to 10 years of age varied from eight ears with no VT insertions up to 14 ears with seven VT treatments. See publication I table 4 and fig. 2.

There was no significant correlation between the number of VT treatments and PTA4 or PTAHF for each ear, at > 7-10 years of age (Pearson Correlation test).

Four of the 29 VT treated children exhibited complications. Two children required a myringoplasty due to persistent perforation of the ear drum; one child (no. 26) had previously undergone four and the other child (no. 15) two VT insertions in the ear with the perforation. The hearing thresholds in these two children showed a PTA4 ≤ 20 dB HL at both age span. Regarding the PTAHF at > 7-10 years, the child with four VT treatments had a threshold at 15 dB HL bilaterally at 6000 Hz, and the child with two VT treatments had a PTAHF ≤20 dB HL bilaterally.

One child (no. 31) with an implantation cholesteatoma in the left ear at 7 years of age, had undergone four VT treatments. Surgery with myringoplasty was performed but a retraction pathology required revision surgery three years later. This child presented with normal PTA4 at both age spans, but a hearing impairment in the higher frequencies bilaterally. The PTAHF at 4-7 years of age was 40 dB HL for the left and 45 dB HL for the right ear, and at > 7-10 years 40 dB HL bilaterally. Another child (no. 32) developed retraction pathology and a cholesteatoma in pars tensa at 15 years of age. The child had gone through two VT treatments in this ear, and at 4-7 years of age had a PTA4 of 21 dB HL but missing data for PTAHF. Between > 7-10 years of age, the child presented with normal PTA4 and a mild, bilateral hearing impairment in the high frequencies. See table 5.

Table 5. Individual data regarding PTA4 and/or PTAHF > 20 dB HL at 4-7 and > 7-10 years, and the number of VT treatments these children had undergone. (PTA4=Pure Tone Average 500, 1000, 2000 and 4000 Hz, PTAHF=Pure Tone Average High Frequencies 6000 and 8000 Hz, VT=Ventilation Tube, m.d.= missing data).

Child	PTA4 4-7	PTA4 7-10	PTAHF 4-7	PTAHF 7-10	no VT
2 RE	36	9	38	25	6
LE	49	5	48	28	7
4 RE	33	10	43	23	7
LE	10	8	13	23	5
6 RE	19	20	45	53	2
LE	24	21	58	48	2
7 RE	24	24	13	18	2
LE	22	15	15	18	3
17 RE	16	8	m.d.	18	3
LE	23	13	m.d.	15	3
18 RE	39	36	40	55	2
LE	11	0	8	5	3
19 RE	15	8	m.d.	10	5
LE	10	15	m.d.	28	3
20 RE	11	21	m.d.	13	1
LE	11	18	m.d.	8	1
21 RE	14	5	23	13	3
LE	6	1	23	10	3
22 RE	23	6	m.d.	13	1
LE	20	3	m.d.	13	1
27 RE	9	8	20	8	4
LE	20	5	23	13	5
28 RE	14	10	28	13	6
LE	11	14	15	10	6
31 RE	9	8	45	40	3
LE	10	11	40	40	4
32 RE	21	20	m.d.	23	2
LE	15	16	m.d.	23	1
35 RE	10	5	m.d.	18	1
LE	11	10	m.d.	23	1
36 RE	6	3	10	15	2
LE	9	11	23	8	2

5.2 Study II

5.2.1 ABR

The neonatal median ABR-thresholds was 35 dB nHL (range: 20-45) in the group of children with cleft palate and 30 dB nHL (range: 20-45) in the group without. Statistical analysis showed no significant difference between the groups (see fig.3).

5.2.2 Audiometry

In the longitudinal group, the comparison of the median 4FA between the two groups exhibited a significant difference only at 12 months of age ($p < 0.01$). At this age the children in the CP±L-group had a median 4FA of 22.5 dB HL compared to 31 dB HL in the group without cleft. Furthermore, there was a significant difference at the discrete frequencies 500 Hz and 4000 Hz at this age, see table 6.

Table 6. 12 months median 4 FA and median thresholds with range within parenthesis
** = p < 0.0.1, Mann-Whitney U test

	CP±L	Without CP±L
Median 4FA	22.5 (20-39)	31 (24-41) **
Median 500 Hz	25 (20-45)	35 (30-45) **
Median 1000 Hz	25 (20-45)	30 (25-40) n.s.
Median 2000 Hz	25 (20-35)	30 (20-40) n.s.
Median 4000 Hz	20 (20-30)	30 (20-50) **

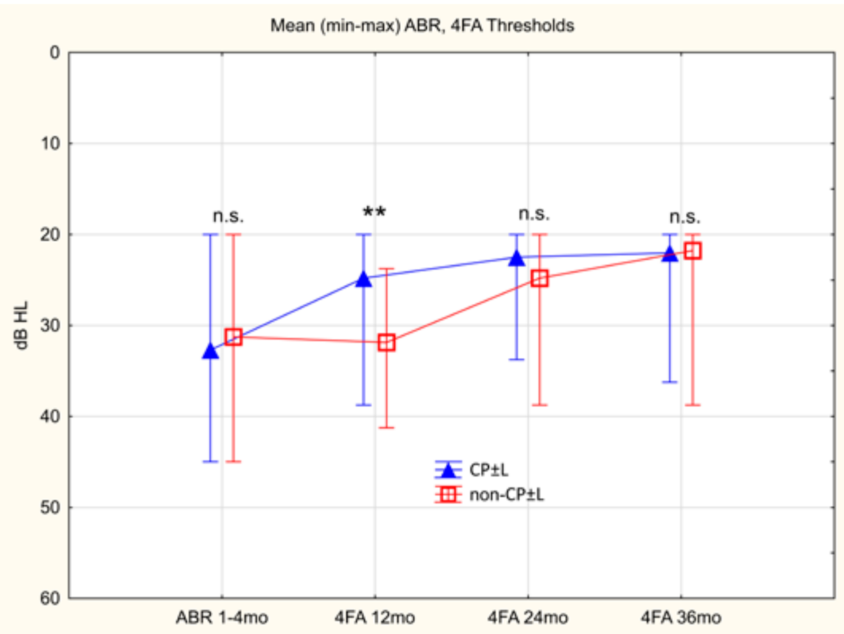
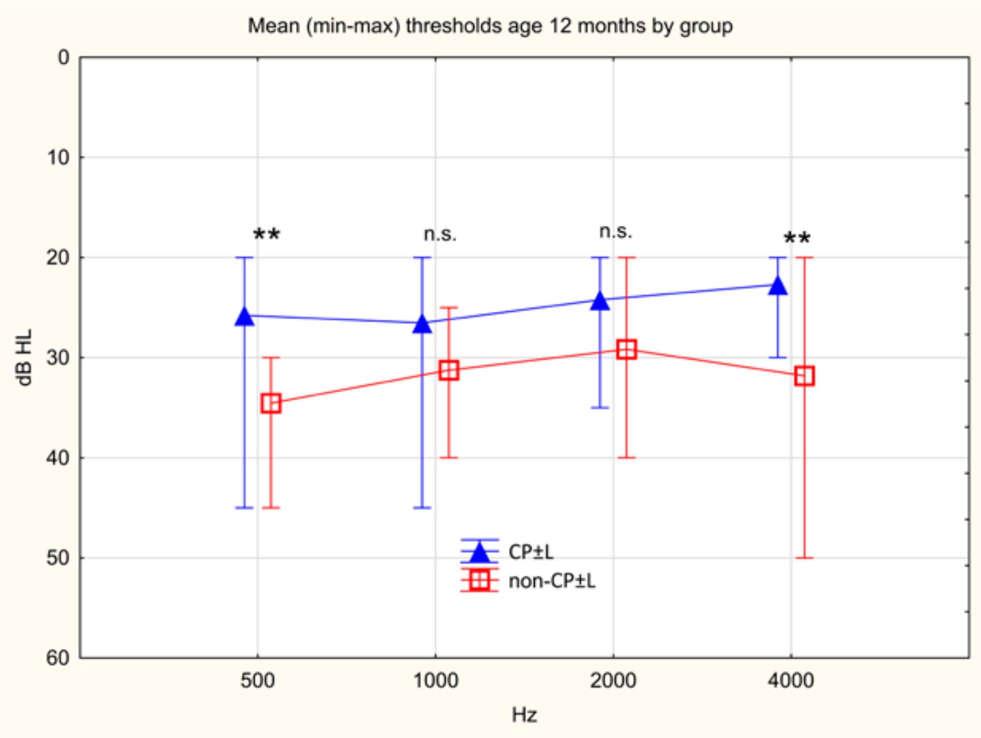
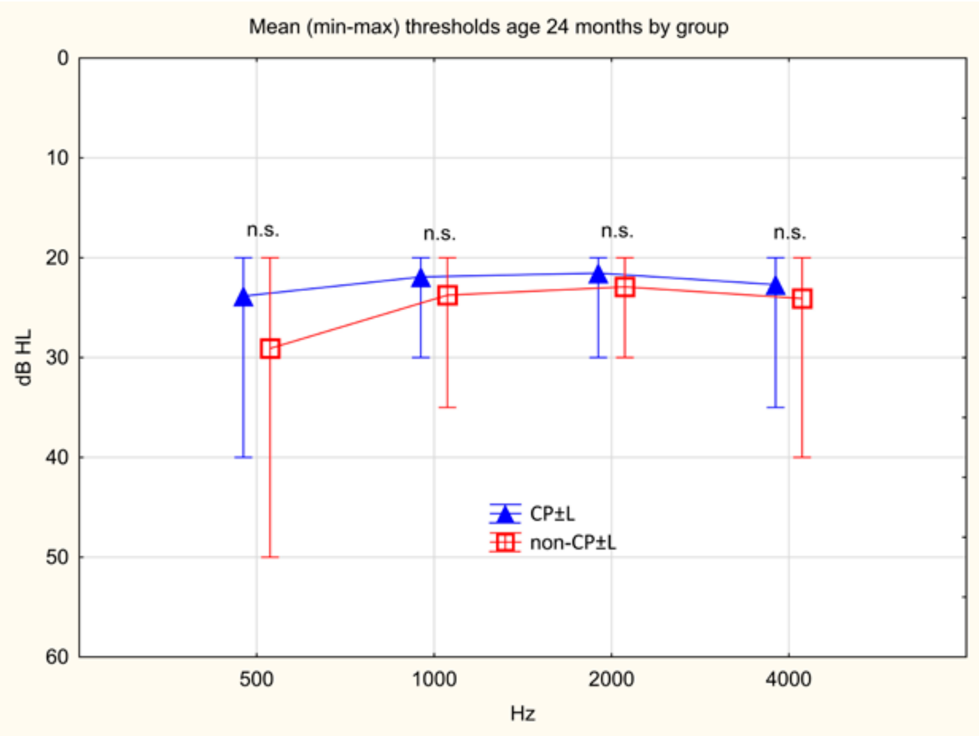


Figure 3. Mean neonatal ABR thresholds in dB nHL (CP±L n=16; non- CP±L n=15) and 4FA at 12, 24 and 36 months of age (CP±L n=13; non- CP±L n=12) per group. **= p < 0.01, Mann-Whitney U test

The statistical analyses did not reveal any significant group differences at 24 and 36 months of age in 4 FA or at any of the discrete frequencies 500, 1000, 2000 and 4000 Hz. Non-parametric methods were used but for illustrational purposes the mean values are presented in the figures 3 and 4a-4c.





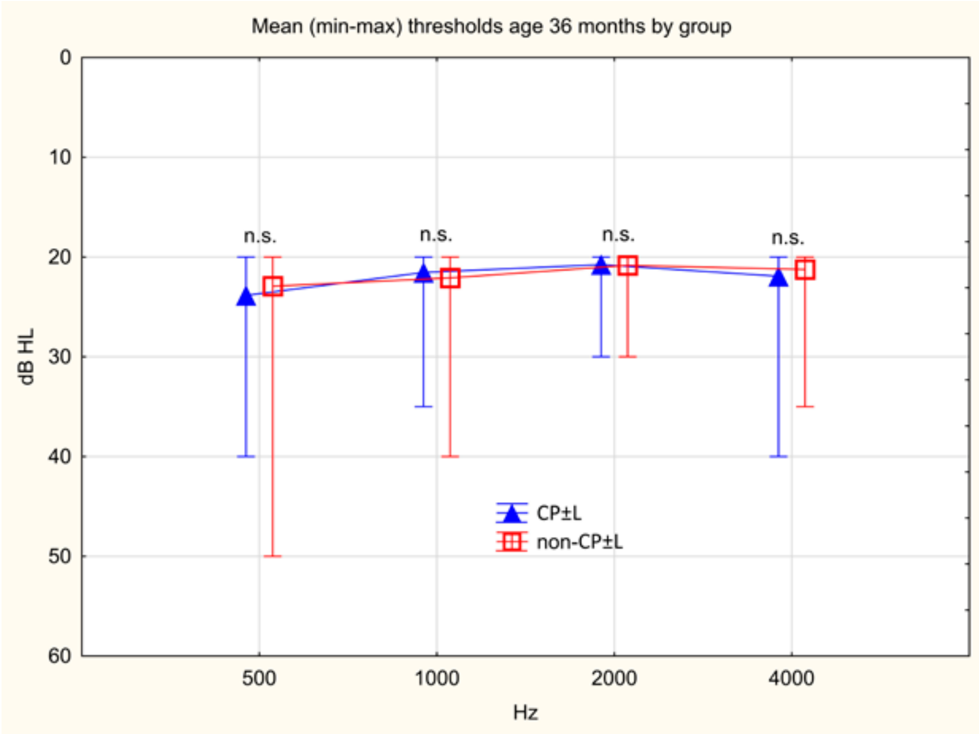


Figure 4 a-c Mean thresholds at 500, 1000, 2000 and 4000 Hz per group at 12, 24 and 36 months of age (n=25). **= *p < 0.01, Mann Whitney U test*

Friedman analysis of variance was performed to examine if air conduction thresholds improved over time. A significant improvement was shown from the neonatal ABR-test to the test at 36 months of age, $p < 0.05$ in CP±L-group; $p < 0.001$ in group without CP±L. When analysing the thresholds from 12 months to 36 months of age, there was a significant improvement in the group without CP±L ($p < 0.001$), but not in the cleft group.

A group-wise comparison was performed of the proportion of subjects designated as pass or fail result at the neonatal ABR test and at each of the 7 different test occasions. The Fisher exact 2-tailed test was used, and the analyses showed no significant between-group differences at any age.

6 DISCUSSION

6.1 Hearing sensitivity

Study I

In this retrospective study on children with UCLP, the comparison of hearing thresholds in the speech frequencies 500 - 4000 Hz demonstrated a significant improvement with age. The proportion of children with 4PTA > 20 dB HL in at least one ear declined from 4-7 years of age to > 7-10 years of age. The comparison of the thresholds in the higher frequencies, 6000-8000 Hz, could not display an improvement in proportions of children with PTAHF > 20 dB HL in at least one ear. The improvement of hearing thresholds in the speech frequencies are in concordance with the findings in several earlier studies on children with CP±L (Skuladottir et al., 2015). The declining frequency of OME-related hearing impairment in the speech frequencies is hypothesized to be due to the declining frequency of OME with age. In a study by Handzic-Cuk (Handzic-Cuk et al., 2001) the decreasing frequency of type B tympanograms with age correlated with better hearing thresholds with age.

In the present study, the findings with no improvement at 6000-8000 Hz are comparable to a study by Flynn et al, in which the PTAHF at 7, 10, 13 and 16 years of age were compiled, and the analyses did not reveal any significant improvement with age (Flynn et al., 2013).

In the current study two children had the first VT-insertion before six months of age, 19 children before two years of age, 7 children before four years of age and one child after four years of age. Four children had no VT treatment. There was no significant correlation between number of VT insertions and the PTA4 and PTAHF for each ear at > 7-10 years of age (Pearson Correlation test).

The prevalence of persistent perforation of the eardrum (6.1%) and acquired cholesteatoma (6.1%) in the study, was in line with the range reported in the literature (Kuo et al., 2014). Spilsbury and colleagues (2013) examined a cohort of 56,949 children who had undergone at least one VT treatment. Cholesteatoma was developed in 6.9% of the children with cleft palate by 18 years of age compared to 1.5% of children without cleft palate. In a retrospective cohort study on 2737 children with various cleft palate the incidence of acquired cholesteatoma was 2.2% between 5 and 18 years of age (Harris et al., 2013).

Many studies have described a relationship between the number of VT treatments and higher hearing thresholds and higher incidence of complications, such as perforation of the eardrum and cholesteatoma (Ryding et al., 2005; Sheahan et al., 2003). If these sequalae are caused by the chronic and protracted disease, or if the VT treatments can increase the risk for these consequences is unclear because they are often concomitant. Children with more severe and protracted disease are treated more often with VT than those with shorter duration of the disease. Furthermore, both VT-insertion, Eustachian tube dysfunction and chronic otitis can cause myringosclerosis, retraction and perforation of the ear drum.

Study II

A comparison of the hearing thresholds between the two groups of children, could not provide evidence for worse hearing thresholds in the group of children with cleft palate. The statistical analysis of the median ABR thresholds did not reveal any significant difference between the two groups which is analogous with a study by Sundman et al. (2016). The significantly better thresholds at 12 months in the group with CP±L is likely due to the early treatment with ventilation tubes in the cleft group at this age. The children without cleft palate had ventilation tubes inserted later, and at 24 and 36 months of age there was no significant group-wise difference regarding hearing thresholds. The hearing thresholds, from the neonatal ABR thresholds to 36 months of age showed a significant improvement over time in both groups. Since ABR thresholds are not directly analogous with behavioral thresholds an analysis was also performed from 12 to 36 months of age, with significant improvement only in the group without cleft. The comparison of the pass to fail ratio between the two groups did not show any significant group-wise difference at any test occasion.

Early routine insertion of VT before the time of palatal repair has been widely discussed. In a controlled prospective study on 39 children with cleft palate and controls with OME but without cleft, all children had ventilation tubes before 7 months of age (Valtonen et al., 2005). At follow-up six years later, the mean pure tone average and otological outcome were similar in the groups. On the other hand, protocol with selective tube placement has been recommended in children with hearing loss or symptomatic infection, instead of routine tube placement at the time of palatal repair, due to findings of no difference in incidence of persistent conductive hearing loss with a selective, compared to routine tube placement (Phua et al., 2009). In a retrospective study by Shaffer and colleagues on 318 children with cleft palate, the impact of hearing loss and timing of VT insertion on speech outcomes was analyzed. Hearing loss after multiple tube treatment were associated with speech and language delays, but there was no evidence to support VT before palatoplasty (Shaffer et al., 2017).

Hearing aids can be an alternative for the management of OME-associated hearing loss in children with treatment resistant otorrhea after VT insertion or when general anesthesia for insertion of VT is not recommended. Comparisons between treatments with VT and hearing aids in children with cleft palate has been presented in a study by Gani et al. The authors recommend a protocol which combines the short-term benefit of VT insertion with the lower complication rate of HA (Gani 2012).

In the longitudinal study, nine of the children with cleft palate had VT in place at 12 months of age, but none of the children in the group without cleft palate had undergone VT insertion at this age. At 24 months of age four of the children without and nine of the children with cleft palate had VT in at least one ear, and at 36 months of age eight children without and six children with cleft palate had VT in at least one ear. The early treatment with ventilation tubes in CP±L group compared to the group without cleft palate did not result in any significant difference in median 4 FA at 24 months, and the median 4FA at 36 months was normal in both groups. However, the two study groups were small, and a significant difference in 4FA at 24 and 36 months of age might have been revealed with a larger number of participants.

6.2 Methodology discussion and Limitations

In study I the follow-up of the children with data about OME and recurrent acute OME was documented by the local ENT in some children, and due to different clinical routines, data about middle ear status was not always available at the time of the hearing assessment. Therefore, it was not possible to adequately examine how the severity and time with OME affected the hearing thresholds, indicating some uncertainty. Furthermore, the study is retrospective, and data may have been incomplete due to a missed appointment.

The aim in study II was to describe hearing thresholds in children with CP±L compared with children with OME but without CP±L. In the longitudinal methodology in study II, the children in both groups were monitored closely from early infancy and followed up to 3 years of age. The aim was to collect more accurate data on hearing from newborn hearing screening until 3 years of age and to be able to make group-wise comparisons. By comparing two groups of children without any associated syndromes, anomalies or other physical impairment, the risk for developmental delays and non-compliance in the test situation decreased. Furthermore, the prevalence of sensorineural hearing loss is higher among children with associated syndromes, for example Sticklers syndrome and van der Woudes syndrome.

In study II the children were very young, and the child´s compliance had impact on the result. The different tests´ abilities to detect small differences in hearing thresholds might have had an influence on the result. Missing data due to missed appointment decreased the number of participants, and small differences between the two groups might have been undetectable.

A comparison of mean and median values between two groups may be misleading if the distribution consists of many outliers. This is often the case in a group of children with middle ear disease regarding the prevalence of complications as permanent hearing loss and abnormalities in the middle ear. Therefore, clinical outcomes of the children with complications should be studied separately to enhance the knowledge about how to treat children with cleft palate.

7 CONCLUSION AND CLINICAL IMPLICATIONS

Assessments of hearing thresholds in children with cleft palate are important in order to evaluate the severity of potential OME related hearing loss. These two studies demonstrated improved thresholds in the speech frequencies at 500-4000 Hz with age. In the higher frequencies, the group-wise comparison in study I did not reveal any significant improvement with age.

In the prospective longitudinal study, the better hearing thresholds at 12 months of age in the group with cleft palate, probably due to early VT insertion might have benefits for early speech and language development. This result should be followed up with further longitudinal studies. The high prevalence of OME and the risk for hearing impairment at early age during the period of early speech and language development, implies that children with cleft palate requires close follow-up with audiological and otological examinations to ensure that hearing impairment is managed appropriately.

To improve the healthcare of children with cleft palate, an evidence-based consensus concerning the treatment of otitis media and the following conductive hearing loss is needed.

8 FUTURE RESEARCH

Study II is part of a prospective longitudinal project on the early development of speech, language, and hearing (TUTH – Tidig Utveckling av Tal och Hörsel) (Lohmander, 2013), in children with OME with or without cleft palate. In the next part babbling, consonant proficiency, and vocabulary will be analyzed. The results will add to an evidence-based consensus about the best way to treat children with cleft palate and OME. However, in order to fully understand the relationship between hearing thresholds and early speech and language development in children with CP±L prospective, randomized, multicenter, longitudinal studies are needed. Future research with standardized management protocols with close follow-up of middle-ear disease, hearing thresholds and speech- and language development will hopefully shed more light on this issue

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