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Central auditory nervous system dysfunction in infants with non-syndromic cleft lip and/or palate

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ABSTRACT

Objective: Peripheral hearing loss has been commonly reported in children with non-syndromic cleft lip and/or palate (NSCLP) but few studies have provided information about central auditory nervous system (CANS) functioning for this group. The main objective of this study was to explore CANS functioning in infants with NSCLP through analysis of auditory evoked potentials (AEPs).
Methods: AEPs including auditory brainstem response (ABR), middle latency response (MLR), and mismatch negativity (MMN) recordings were conducted in 34 infants of Chinese ethnicity with NSCLP and an equivalent number of normal controls.
Results: There was no significant difference in ABR (all measurements, including wave I, III, V latencies, I–V inter-wave latency, and wave V amplitude), or MLR (recordable components, Na, Pa latencies, and Na–Pa amplitude) findings between the two groups. However, infants with NSCLP had a significantly smaller MMN response than their normal controls, using MMN strength as the measurement.
Conclusions: Significant abnormal auditory evoked potential findings at the cortical level suggest that infants with NSCLP may be at risk of central auditory discrimination dysfunction. Further effort is needed to determine auditory processing abilities in infants with NSCLP.

1. Introduction

The treatment objectives for children with cleft lip and/or palate (CL/P) target normal physical and social-psychological development. Normal speech and hearing functions are crucial for developing age-appropriate communication skills in children with CL/P. Hearing impairment has been reported as a common co-morbidity with craniofacial clefts and the presence of peripheral hearing loss in this group has been well documented. However, most reports only focus on the effects of middle ear disease and conductive hearing loss in patients with CL/P [1]. To date, data on higher level auditory function in children with CL/P are limited. One possible reason might be that middle ear disorders are very common in children with CL/P and symptoms are readily noted by clinicians, while more subtle hearing disorders could be overlooked [2]. However, hearing is a complex process, which includes the conduction, perceptual registration and cognitive elaboration of acoustic signals by the brain as well as conscious perception of sound [3]. Hearing impairments, whether arising from pathology of the middle or inner ear, or from dysfunction of the central auditory pathway, may have detrimental consequences on a child's life if untreated. Recent studies have reported possible cortical auditory impairment—reflected by abnormal auditory event-related potentials (ERPs)—in children with craniofacial abnormalities, including both syndromic and non-syndromic cleft lip and/or palate (NSCLP) children [4,5]. Children with NSCLP have also been noted to have some overt behaviors indicative of auditory processing disorder (APD) [6]. In addition, structural brain abnormalities have been reported in patients with NSCLP. Nopoulos et al. [7] noted structural brain abnormalities in adult males with NSCLP based on magnetic resonance image (MRI) scanning results and found that NSCLP subjects had significantly lower temporal lobe gray matter volume than matched controls. The authors further reported that the superior temporal plane (STP) of NSCLP adult male subjects was disproportionately large compared to normal controls in a regional analysis of brain structures [8]. As STP is a brain region believed to be involved in auditory processing, it is worthwhile to investigate whether auditory function is affected by structural STP malformation in individuals with NSCLP. Nopoulos' group also evaluated the brain structure of 74 children and teenagers with NSCLP (aged 7–17 years), and found that they had abnormally small cortical volume

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and different tissue distribution compared with normal peers [9]. They stated that the pattern of brain abnormalities in children with NSCLP was "dramatically" different from that noted in adult subjects with NSCLP, suggesting that brain development might be abnormal in subjects with NSCLP. For infants with NSCLP, research on auditory cortical structure and function remains to be conducted. Studies on the central auditory nervous system (CANS) or auditory pathway of young children with CL/P are warranted.

To evaluate CANS function, auditory evoked potentials (AEPs) for decades have been applied as an objective, noninvasive tool [10]. AEPs are small electrical voltage potentials originating from the CANS in response to auditory stimuli and can be recorded from the scalp [11]. Due to the progressive latency increase of responses from more rostal auditory structures, AEPs are often classified into early response, or auditory brainstem response (ABR, 1.5–10 ms post stimulus), middle latency response (MLR, 25–50 ms post stimulus) and late response or long latency response (LLR, 50–300 ms post stimulus), based on their response time relative to the onset of acoustic stimuli [12]. Unlike speech audiometry and other behavioral auditory tests, AEPs can be recorded regardless of a child's language, motivation, or attention level, and have been considered an appropriate tool to evaluate auditory function in young children [13]. It had been reported that auditory function in children from the eighth nerve to the level of the auditory cortex could be estimated using ABR, MLR and LLR [14–16]. ABR is thought to originate in the 8th cranial nerve (waves I and II) and brainstem (approximately, wave III in cochlear nucleus, wave IV in superior olivary complex, wave V in lateral lemniscus contralateral to the stimulated ear, and waves VI–VII in inferior colliculus) [17]. Study of the generators of MLR showed considerable support for thalamo-cortical projections to primary and secondary auditory cortices [18]. Generators of LLR include late thalamic projections to the early auditory cortex and nonspecific multisensory systems in the supra-temporal auditory cortex [19]. Although LLR responses may be present in infants, they show considerable maturational change, and some cortical potentials may not be fully mature until close to adulthood. These maturational changes limit the use of LLR for diagnosis of CANS dysfunction in young children and infants [20]. However, mismatch negativity (MMN), a component of LLR, has been taken as a suitable tool for studying cortical auditory function in young children as this response is believed to be reliably recorded even in infants [16]. Studies suggest that a major MMN source is located in the auditory cortex, and there is some evidence for a contribution of frontal-lobe activity to the MMN [21]. MMN is an evoked potential elicited using an oddball stimulus paradigm resulting from preconscious perception of a change in the auditory stimulus and hence has been referred to as a processing-contingent potential [22]. It can be elicited by unattended stimuli and children do not have to perform any tasks during the test [23]. In addition, there seem to be only small differences in MMN amplitudes and latencies between different sleep and waking states [24].

ABR and MLR are regarded as sensory or "obligatory" responses that depend on the physical properties of the stimulus, while MMN is a "discriminative" response to an oddball stimulus paradigm [13]. Both obligatory and discriminative potentials have been investigated as objective indices of central auditory function since they correlate well with the perception and discrimination of auditory stimuli. In the current study, ABR, MLR and MMN were selected as tools to estimate sensory and discriminative CANS function in infants with NSCLP.

2. Methods

The current study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority West Cluster (HKU/HA IRB, Protocol Number UW 07-250).

2.1. Participants

Eight one infants with NSCLP, aged from 6 to 24 months, were recruited using a convenience sampling method from the Department of Head and Neck Surgery, Shenzhen Children's Hospital, southern China from September 2007 to August 2008. Clinical history questionnaires were completed for all children who participated in the study, through interview of the parents or caregiver by a certified clinician. The selection criteria were as follows: Full-term birth and uncomplicated delivery (with normal birth history), non-syndromic cleft (no other disorders, e.g., genetic syndromes, ventricle septum defect, perinatal asphyxia), and subjects had no other chronic health disorders. We first conducted middle ear examination (otoscopy plus tympanometry), TEOAE screening and air conduction ABR (click evoked) hearing threshold acquisition. Potential subjects with active middle ear disease (otitis media, or with an abnormal tympanogram), and those who failed TEOAE screening, or with hearing loss (ABR air conduction thresholds $\geq$ 30 dB nHL)—a total of 47 infants with NSCLP—were excluded from the project to reduce the impact of conductive hearing loss on AEP recording.

Tympanometry was conducted using a GSI-33 middle ear analyzer (GSI Corp., WI, USA) with a continuous probe signal of 85 dB SPL at 226 Hz and a sweep rate of 50 da Pa/s. Measures included equivalent ear canal volume, peak compensated static acoustic admittance, tympanometric gradient, and tympanometric peak pressure. Using Jerger's [25] classification of tympanometric results, failure in tympanometry was defined as any result that could be classified as a type B or C tympanogram. TEOAE measurement parameters included signal-to-noise ratios at 1.6, 2.4, 3.2, and 4.0 kHz center frequencies and standard pass/fail criteria were used [26]. At least 50 stimuli were presented to evoke TEOAEs for each ear. If the resulting TEOAE spectrum did not meet the pass criteria, testing was continued until a maximum of 260 stimuli were presented. A TEOAE response at a particular frequency was considered present if the response was at least 3 dB above the noise floor, and responses were obtained in at least three out of four octave frequency bands. In addition, response reproducibility of no less than 50% was required for a pass result; otherwise, a fail result was recorded.

Thirty four NSCLP infants with normal middle ear and cochlear function and normal hearing level were included in this study. The mean age of the NSCLP group was 15.4 months (SD = 5.9 months). Thirty four non-cleft children matched for age and sex (mean age = 15.4 months, SD = 5.9 months), were recruited as normal controls. The purpose of the study was explained to parents and informed consent was obtained from all parents or caregivers of the study participants before testing. Demographic data including age, gender, cleft type, and cleft repair status were recorded. All participants were Han Chinese from southern mainland China and 86% of infants were from families with low socioeconomic status residing in rural areas. 91.2% of the cleft subjects were male, and this gender imbalance might relate to preference for male gender offspring in Chinese families with low socioeconomic status [27]. The sample characteristics of the NSCLP group are summarized in Table 1.

2.2. Auditory evoked potentials recording

The purpose of AEP recording in this study was to identify the characteristics of the CANS response to acoustic stimuli in children with NSCLP and compare to normal control infants. All AEPs recording were conducted in a sound treated room at the hearing center in Shenzhen Children's Hospital, using a SmartEP-ASSR system (Intelligent Hearing System Corp., USA), calibrated to manufacturer recommended standards. The ambient noise level