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REVIEW

SLC26A4 mutation testing for hearing loss associated with enlargement of the vestibular aqueduct

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Abstract

Pendred syndrome (PS) is characterized by autosomal recessive inheritance of goiter associated with a defect of iodide organification, hearing loss, enlargement of the vestibular aqueduct (EVA), and mutations of the *SLC26A4* gene. However, not all EVA patients have PS or *SLC26A4* mutations. Two mutant alleles of *SLC26A4* are detected in 1/4 of North American or European EVA populations, one mutant allele is detected in another 1/4 of patient populations, and no mutations are detected in the other 1/2. The presence of two mutant alleles of *SLC26A4* is associated with abnormal iodide organification, increased thyroid gland volume, increased severity of hearing loss, and bilateral EVA. The presence of a single mutant allele of *SLC26A4* is associated with normal iodide organification, normal thyroid gland volume, less severe hearing loss and either bilateral or unilateral EVA. When other underlying correlations are accounted for, the presence of a cochlear malformation or the size of EVA does not have an effect on hearing thresholds. This is consistent with observations of an *Slc26a4* mutant mouse model of EVA in which hearing loss is independent of endolymphatic hydrops or inner ear malformations. Segregation analyses of EVA in families suggest that the patients carrying one mutant allele of *SLC26A4* have a second, undetected mutant allele of *SLC26A4*, and the probability of a sibling having EVA is consistent with its segregation as an autosomal recessive trait. Patients without any mutations are an etiologically heterogeneous group in which siblings have a lower probability of having EVA. *SLC26A4* mutation testing can provide prognostic information to guide clinical surveillance and management, as well as the probability of EVA affecting a sibling.

Key words: *SLC26A4*; Pendred syndrome; Genetic testing; Goiter; Hearing loss; Vestibular aqueduct; Genotype-phenotype correlation

Core tip: Enlargement of the vestibular aqueduct (EVA) is a common inner ear anomaly. We review the correlation of phenotype with genotype of *SLC26A4*. *SLC26A4* mutations are the most prevalent known cause of hearing loss associated with EVA. The number of mutated alleles is correlated with the presence or absence of a

thyroid iodination defect, thyroid gland volume, severity of hearing loss, laterality (bilateral *vs* unilateral) of the inner ear anomaly, and probability of recurrence of EVA in a sibling. We discuss the risks and benefits of genetic testing and counseling for affected patients. These concepts may be of broad interest to otolaryngologists, audiologists and other clinicians.

Ito T, Muskett J, Chattaraj P, Choi BY, Lee KY, Zalewski CK, King KA, Li X, Wangemann P, Shawker T, Brewer CC, Alper SL, Griffith AJ. *SLC26A4* mutation testing for hearing loss associated with enlargement of the vestibular aqueduct. *World J Otorhinolaryngol* 2013; 3(2): 26-34 Available from: URL: http://www.wjgnet.com/2218-6247/full/v3/i2/26.htm DOI: http://dx.doi.org/10.5319/wjo.v3.i2.26

PENDRED SYNDROME AND NONSYNDROMIC HEARING LOSS WITH ENLARGEMENT OF THE VESTIBULAR AQUEDUCT

Pendred syndrome (PS) is characterized by autosomal recessive inheritance of goiter and hearing loss, first reported in two sisters by Pendred[1] in 1896. Fraser[2] estimated this syndrome accounted for 5.6% of congenital hearing loss in his series of 2355 children. The causative gene for PS was mapped to chromosome 7q in 1996[3] and identified as *SLC26A4* in 1997[4]. Molecular testing for *SLC26A4* mutations and temporal bone imaging have established that PS is always accompanied by inner ear deformities, with enlargement of the vestibular aqueduct (EVA) as the most penetrant feature[5] (Figure 1). The identification of *SLC26A4* mutations associated with PS suggested a possible association of nonsyndromic hearing loss with EVA (NSEVA) with mutations of this gene. Usami *et al*[6] identified *SLC26A4* mutations in sporadic and familial cases of NSEVA, showing that *SLC26A4* mutations are commonly associated with NSEVA. These observations were confirmed in numerous studies of large cohorts of PS and NSEVA patients from different ethnic populations[7-11].

Most clinicians now rely upon molecular testing of *SLC26A4* for the etiologic diagnosis of PS and NSEVA. There are over 200 reported mutations in *SLC26A4* associated with sporadic and familial forms of PS and NSEVA. Furthermore, a large-scale study demonstrated mutations of *SLC26A4* in approximately 5%-10% of individuals with childhood deafness among several large global populations[12]. This percentage is coincident with Fraser's phenotypic estimate of the prevalence of PS[2]. However, in North American and European populations, *SLC26A4* mutations cannot be detected in up to one half of patients with hearing loss and EVA, while only one mutant *SLC26A4* allele is identified in one fourth of patients[9-11,13]. EVA has also been detected in a subset of patients with branchio-oto-renal or branchio-oto syndrome[14], Waardenburg syndrome[15], and deafness associated with the recessive form of distal renal tubular acidosis[16]. However, there is no published evidence that mutations of the genes underlying these syndromes cause PS or NSEVA.

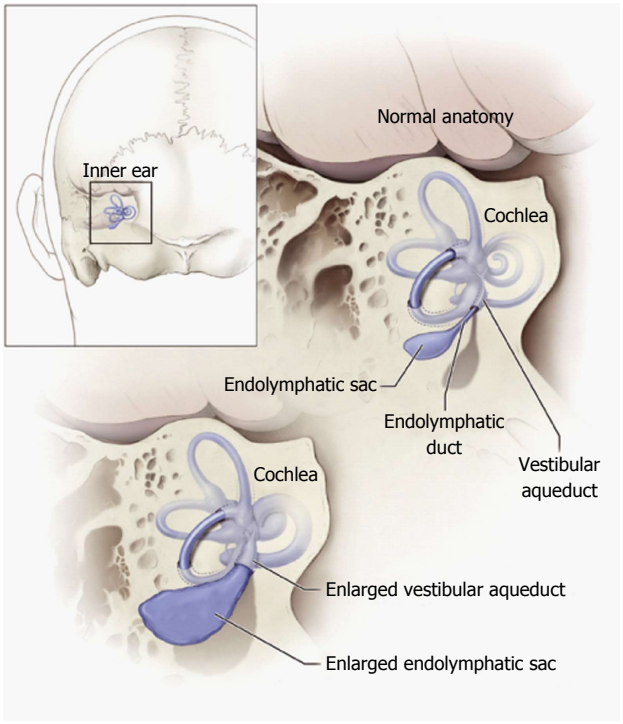

Figure 1 Schematic illustration of the relationship of the vestibular aqueduct with the endolymphatic sac and duct. Normal anatomy of the inner ear structures is shown above. Pathologic enlargement of the endolymphatic sac and abnormal enlargement of the vestibular aqueduct are shown below. Some ears with enlargement of the vestibular aqueduct also have a reduced number of cochlear turns. Reproduced from http://www.nidcd.nih.gov/health/hearing/vestAque.htm.

SLC26A4 encodes a transmembrane protein, called pendrin, comprised of 780 amino acids and 12 or more predicted membrane-spanning domains[4,17-21]. Mouse *Slc26a4* is expressed in a restricted tissue distribution that includes the inner ear, thyroid, kidney, lung, and several other organs[4]. Pendrin has been shown to exchange anions across the plasma membrane in several heterologous expression systems. Physiologically predominant functional modes are thought to include Cl^-/I^- exchange in the thyroid[22] and Cl^-/HCO_3^- exchange in the inner ear[23]. This anion exchange activity is critical during late embryonic and early postnatal development of the inner ear[24]. A variety of cellular details of the pathogenic events have been described[25-28]. Here we summarize the clinical phenotypes, genetics, and a novel mouse model of EVA.

CORRELATION OF *SLC26A4* GENOTYPE WITH THYROID PHENOTYPE

The pathogenesis of goiter in PS is thought to be a thyroidal iodine organification defect[29]. The goiter tends to be diffuse at first, but later becomes nodular[2]. The organification defect can be detected by measuring the discharge of inorganic radioiodide from the thyroid after adminis-

tration of potassium perchlorate. Potassium perchlorate is a competitive inhibitor of the sodium-iodide symporter, which transports iodide into thyroid folliculocytes across their basolateral membrane. An abnormally high discharge of iodide from the thyroid gland in response to perchlorate administration is a relatively specific finding for the clinical diagnosis of PS. For decades, it was the gold standard for the diagnosis of PS. Goiter, an abnormal perchlorate discharge, or both is identified in one third to one fourth of patients with hearing loss and EVA[30,31]. Goiter is an incompletely penetrant feature of PS. Furthermore, an onset during adolescence is typical[2,32]. The distinction between PS and NSEVA can therefore be difficult to make during childhood. This problem is exacerbated by the insensitivity of the physical examination for detection of goiter. While ultrasound examination with volume determinations may be helpful, normal gland size varies with age, and volume determinations have typically not been reported in a normalized fashion. In addition, goiter of other etiologies is common in some regions and populations, leading to phenocopies that increase the potential for misdiagnosis[33].

SLC26A4 mutations are responsible for both PS and some cases of NSEVA, which suggested a possible correlation between particular types of mutations and the presence of the goiter[8,34]. Scott *et al*[7] concluded that normal thyroid function in NSEVA patients is the consequence of residual pendrin activity encoded by hypofunctional *SLC26A4* variants as compared to functional null alleles in PS patients. However, subsequent studies of cohorts with EVA and hearing loss failed to support this hypothesis[8,35]. Alternatively, a correlation between clinical phenotype and the number of mutant alleles of *SLC26A4* has been suggested. With a definition of PS as > 15% discharge of iodide 2 to 3 h after administration of perchlorate, there was strong correlation between PS and the presence of two (M2) mutant *SLC26A4* alleles, while NSEVA was associated with either one (M1) or zero (M0) mutant alleles[9,10]. Moreover, a multivariate analysis concluded that thyroid gland volume is primarily dependent on the presence of two mutant alleles of *SLC26A4*, at least in pediatric (< 10 years old) EVA patients[30].

CORRELATION OF *SLC26A4* GENOTYPE WITH AUDITORY PHENOTYPE

Radiologically detectable inner ear deformities are often considered to be pathologic changes that contribute directly to congenital deafness. Inner ear deformities were first reported by Mondini[36] in a temporal bone histopathological study in 1791. For centuries afterwards, the term "Mondini dysplasia" was often used for any inner ear malformation. Over many years, the classification and interpretation of inner ear anomalies, especially cochlear deformities, were based on a linear developmental model in which a developmental arrest occurred during embryogenesis[37,38].

However, certain observations do not support the developmental arrest model for all inner ear malformations.

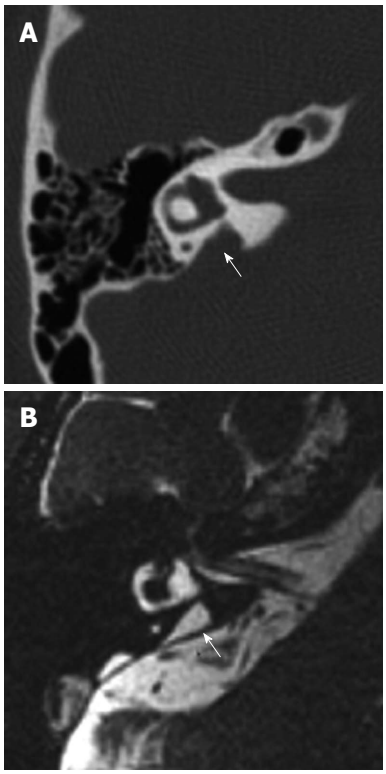

Figure 2 Right temporal bone of a patient with enlargement of the vestibular aqueduct. A: Axial computer tomography image of a right temporal bone with an enlarged vestibular aqueduct (arrow); B: Equivalent magnetic resonance image of the same temporal bone showing an enlarged endolymphatic duct (arrow). Reproduced from http://www.nidcd.nih.gov/health/hearing/Pages/eva.aspx.

The vestibular aqueduct (VA) is a narrow bony canal that opens onto the medial surface of the temporal bone and contains the endolymphatic sac and duct (Figure 1). The VA continues to grow throughout fetal life, but does not reach its full mature size before birth[39]. Some temporal bone studies indicate that the VA continues to grow postnatally in size until 3 years of age[40,41]. These observations were inconsistent with the hypothesis of arrested development[38]. Kim *et al*[42] reported that EVA and scala media expansion occurred at embryonic day 14 in the *Slc26a4*-null mouse model. Their model postulated that enlargement depends on disruption of the normal balance between endolymph secretion and absorption in the labyrinth and endolymphatic sac. They speculated that lumen enlargement might be a form of hydrops caused by increased endolymphatic osmotic pressure due to impaired resorptive ion transport. This observation suggested that a developmental distortion, as well as arrest, occurs during fetal embryogenesis, thus explaining the concomitance of EVA and Mondini dysplasia.

EVA in humans is conventionally defined as a VA diameter exceeding 1.5 mm, measured at the midpoint between the common crus and external aperture (Figure 2). This original radiologic criterion was proposed by Valvassori *et al*[43] in 1978. A recent study demonstrated that 1.0 mm is a more sensitive criterion for EVA[44]. EVA can occur as an isolated anomaly, as well as in combination with other

inner ear deformities[45,46]. Inner ear deformities have been detected in 20%-30% of patients with congenital deafness[46-49]. EVA is the most common inner ear deformity, recognized in approximately 5%-15% of ears of deaf children[49-52].

No significant association has been reported between the type or number of mutant alleles of *SLC26A4* and the presence of cochlear anomalies[10,45,53]. In contrast, two mutant alleles of *SLC26A4* (M2) are tightly correlated with bilateral EVA, while unilateral EVA is correlated with only one (M1) or zero (M0) mutant allele of *SLC26A4*[9]. Unilateral EVA is found with and without other inner ear deformities and is two to six times less frequent than bilateral EVA in North American and European populations[34,54-56].

The hearing loss associated with *SLC26A4* mutations is predominantly sensorineural or mixed, asymmetric, with an onset in the first few years of life. The degree of hearing loss can vary from mild to profound[31,38,45,55]. The hearing loss often shows fluctuation and overall downward progression that can be precipitated by minor head trauma or barotrauma. Hearing loss progression has been observed in 36%-88% of ears and fluctuation has been observed in 30%-92% of ears associated with *SLC26A4* mutations[10,31,45]. Almost one half of the ears with fluctuating hearing loss eventually showed overall progressive loss of hearing. Even in the ears with normal to moderate hearing loss, hearing loss could progress at the rate of about 1 dB/year, with no apparent effect of environment factors[45].

No significant relationship has been reported between the degree of hearing loss and the type of mutation or the presence of cochlear deformities, whereas the degree of hearing loss associates significantly with the number of mutant alleles of *SLC26A4*[9,10,45,55]. The presence of two mutant alleles (M2) is associated with more severe hearing loss than only one (M1) or zero (M0) mutant alleles. Most reports have failed to reveal significant effects of number of mutant alleles of *SLC26A4* or the presence or absence of cochlear anomalies on longitudinal hearing[10,45]. The degree of hearing loss does not correlate with the degree of enlargement of the VA or its contents, the endolymphatic duct[45,57]. This strongly suggests that endolymphatic hydrops is not a direct cause of hearing loss. Although others have reported potential correlations of radiologic findings with hearing loss phenotypes[58], these conclusions were based upon univariate analyses that did not account for underlying factors and correlations such as *SLC26A4* genotype, age, and other genetic diagnoses.

PATHOGENESIS OF HEARING LOSS ASSOCIATED WITH EVA

Although hearing loss is often sensorineural, bone conduction threshold testing can reveal a mixed (conductive plus sensorineural) hearing loss at low frequencies associated with normal tympanometry and middle ear findings[59-62], and an abnormal vestibular evoked myogenic potential result[63]. These findings are thought to be due to a "third window" effect upon sound transmission within the labyrinth[64].

The pathogenesis of sensorineural component in hearing loss ears with EVA has been enigmatic. It was initially believed that trauma or barotrauma increases intracranial pressure with reflux of the contents of the endolymphatic sac and duct into the scala media through the enlarged endolymphatic duct. However, there is little evidence to support this theory, as obliteration of the endolymphatic sac and duct does not reverse or even prevent further hearing loss in patients with EVA[38]. It has also been suggested that sudden drops of hearing might be caused by rupture of Reissner's membrane[38], hemorrhage in the endolymphatic sac[65] or a fistulous round window membrane[66]. There may be occasional examples of these pathogenic mechanisms, but recent research indicates that the underlying mechanism is more often attributable to an intrinsic disruption of endolymphatic homeostasis.

Studies of an *Slc26a4*-null mouse model suggested scala media expansion and endolymphatic acidosis are early consequences of a lack of pendrin expression[67,68]. Subsequently, oxidative stress, abnormal cell stretching, impaired cell-to-cell communication, and loss of KCNJ10 expression occur in the stria vascularis, associated with a reduced endocochlear potential (EP) and hearing loss[23,69-71].

Slc26a4 is expressed in multiple non-sensory cell populations of the cochlea, vestibular labyrinth, and endolymphatic sac and duct[70,72,73]. The *Foxi1* gene encodes a forkhead transcription factor[74], which regulates transcription of *Slc26a4* in the endolymphatic sac and duct[75-77], but not in the cochlea or vestibular labyrinth. The observation of EVA and deafness in a *Foxi1*-null mouse, in which pendrin is expressed in the cochlea and vestibular labyrinth but not in the endolymphatic sac, suggested that pendrin expression in the endolymphatic sac is essential for the acquisition of normal hearing[75].

Slc26a4- and *Foxi1*-null mice are profoundly deaf with severe inner ear malformations and degenerative changes that do not model the less severe human phenotype. Choi *et al*[24] reported a binary transgenic mouse line with doxycycline-inducible pendrin expression, in which pendrin expression during embryonic day 16.5 to postnatal day 2 was necessary and sufficient to acquire normal hearing at 1 mo of age. Lack of pendrin during this period could lead to endolymphatic acidification, loss of the EP and mild to severe hearing loss, even without significant scala media expansion or EVA. The timing of pendrin expression could be manipulated to generate mice with unilateral or asymmetric hearing loss associated with minimal, if any, EVA and no other morphogenetic anomalies (Figure 3). Since this latter model more closely approximated the human phenotype, endolymphatic acidification appears to be more important than scala media expansion for the pathogenesis of hearing loss. Although there are no histopathological specimens from patients with isolated EVA to corroborate these observations in mouse models, it seems doubtful that endolymphatic hydrops plays a direct causative role in the hearing loss associated with EVA[78].

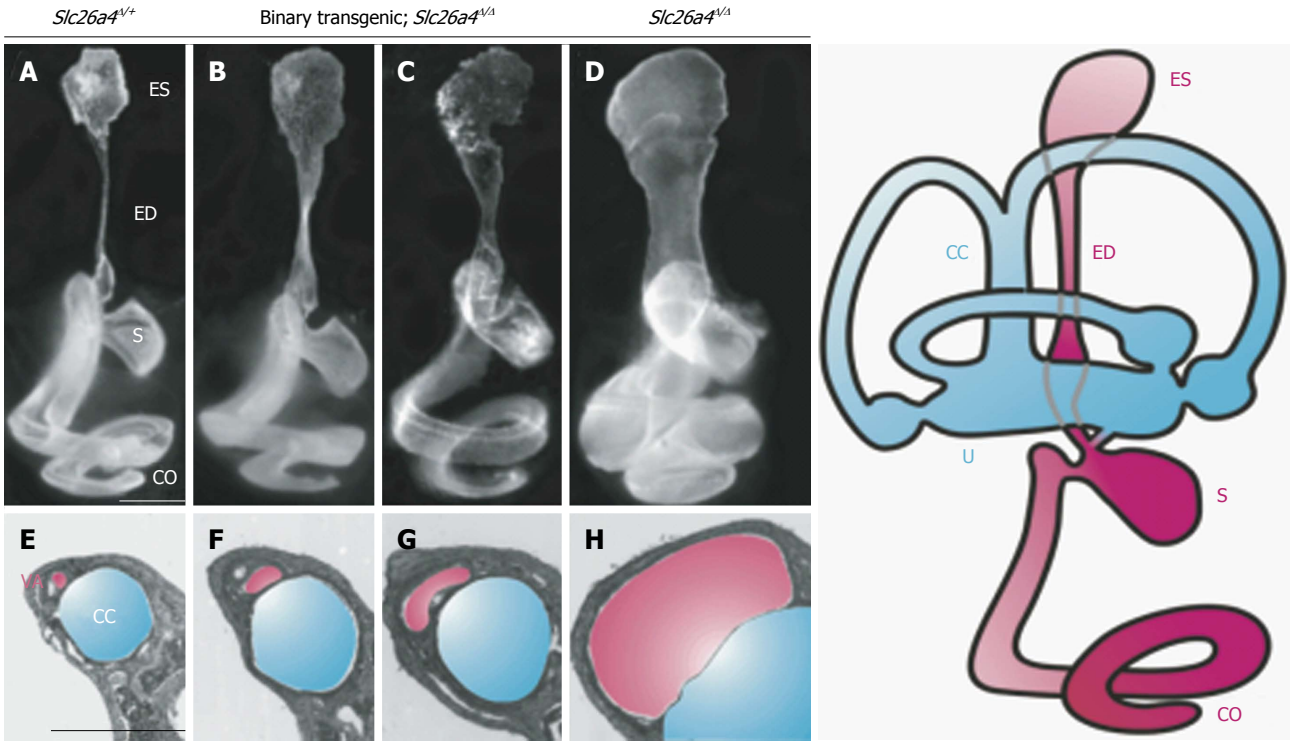

Figure 3 Morphology of the endolymphatic sac and duct and vestibular aqueduct in *Slc26a4* mutant mouse models of enlargement of the vestibular aqueduct. *Slc26a4*$^{\Delta/+}$ normal control (A and E), binary transgenic;*Slc26a4*$^{\Delta/\Delta}$ (B, C, F and G), or *Slc26a4*$^{\Delta/\Delta}$ mutant control mice (D and H) were sacrificed at P3 for paint-fill analysis (A-D) or between P28 and P109 for cross-sectional histopathology of the vestibular aqueduct (VA, shaded pink) adjacent to the common crus (CC, shaded blue; E–H). Scale bars: 500 μm (A, applies to A–D; E, applies to E–H). Manipulating pendrin expression in binary transgenic; *Slc26a4*$^{\Delta/\Delta}$ mice results in less enlargement of the endolymphatic duct and sac and vestibular aqueduct (B, C, F and G). ES: Endolymphatic sac; ED: Endolymphatic duct; S: Saccule; U: Utricle; CO: Cochlea. Reproduced with modification from Choi *et al*[24].

ETIOLOGY OF EVA IN PATIENTS WITH NON-DIAGNOSTIC *SLC26A4* GENOTYPES

A single mutant allele of *SLC26A4* is unlikely to be sufficient to cause hearing loss and EVA. There are no published reports of vertical co-segregation of EVA with a single mutant allele of *SLC26A4* or of sporadic cases associated with a single *de novo* mutant allele of *SLC26A4*[9]. To elucidate the genetic causes and recurrence probability of EVA in families of probands with non-diagnostic *SLC26A4* genotypes (M1 or M0), Choi *et al*[79] compared segregation ratios of EVA in M1 and M0 families with M2 families. A segregation ratio is a measure of the frequency of the phenotype among a proband's siblings and, thus, provides an estimate of recurrence probability in siblings. The segregation ratio of EVA in M1 families was not significantly different from that in M2 families, consistent with the predicted ratio (25%) for an autosomal recessive trait with full penetrance and viability. The results suggested the existence of a second, undetected *SLC26A4* mutation in the M1 families[79]. It is also possible that a single pathogenic mutation of *SLC26A4* might cause EVA in combination with a mutation in another gene[9]. Yang *et al*[80] described digenic heterozygosity for mutations of *SLC26A4* and *FOXI1*[77] or *KCNJ10* in EVA patients. However, these results have not been reproduced in other studies of EVA cohorts[54,81-83] and the pathogenic potential of *FOXI1* and *KCNJ10* variants thus remains undetermined[84,85]. Furthermore, *SLC26A4*-linked polymorphic DNA markers co-segregated with EVA in M1 families. This result is consistent with the hypothesis that current mutation analyses are failing to detect mutations that affect *SLC26A4* or its expression on the apparently wild type allele of *SLC26A4* in M1 families. Taken together, the data suggest that there is a second, undetected mutation of *SLC26A4* that alters a promoter or enhancer or creates a cryptic splice site within an intron. Alternatively, epigenetic modifications of *SLC26A4* such as DNA methylation might repress transcription[86] and account for the observed co-segregation of EVA and *SLC26A4* in M1 families. The correlation of the absence of goiter, and less severe inner ear deformities and hearing loss with M1 genotypes may reflect undetected mutant or epigenetically-modified alleles of *SLC26A4* that act as hypomorphic alleles with residual function[79], in a tissue- or time-specific manner[24], or a combination of these mechanisms.

In M0 families, the segregation ratio was significantly lower than in M2 families and there was discordant inheritance of *SLC26A4*-linked DNA markers with EVA. These results suggested etiologic heterogeneity that includes environmental causes, mutations in other genes, or a combination of these factors[79]. Congenital cytomegalovirus (CMV) infection can produce a very similar auditory phenotype to that associated with EVA[87]. However, congenital CMV infection was ruled out as a common or significant cause of EVA[88].

GENETIC TESTING FOR EVA

Most patients want to know the cause of their hearing loss and have a positive attitude toward genetic testing[89-91]. Genetic testing for *SLC26A4* mutations can provide useful information for EVA patients. In some families, it may alleviate parental anxiety or guilt about the cause of hearing loss in their children. Second, it can guide the decision to longitudinally monitor the thyroid gland for enlargement or dysfunction. Third, it can be used to estimate the severity of hearing loss[10,45,55]. Fourth, it provides data for genetic counseling about recurrence probability, and the relative likelihood that EVA would be unilateral or bilateral if it does affect a sibling.

Assuming full viability and full penetrance of EVA in persons with two mutant alleles of *SLC26A4*, the probability of EVA in the sibling of an M2 EVA proband is 25%. Similarly, the probability of EVA in a sibling of a heterozygous (M1) proband with hearing loss and EVA is statistically indistinguishable from that for a sibling of an M2 proband[79]. The probability of EVA in a sibling of an M0 proband is significantly less than that for a sibling of an M1 or M2 proband, although the probability (about 11%) is not zero[79]. In the NIH cohort of EVA subjects, when EVA was observed in M0 sibling pairs, the siblings were often monozygotic or dizygotic twins. It is not clear if this reflects ascertainment bias or a relationship of twinning with the development of EVA.

We conclude that genetic testing for *SLC26A4* mutations can be beneficial for some patients with EVA. However, it should always follow pre-test counseling so that patients and parents understand what testing can and cannot reveal. Pre-test counseling should also include a discussion of potential risks, including the possibility that testing may reveal unexpected biological relationships, implied carrier status in relatives, or potential insurance or employment discrimination. It is rare for otolaryngologists to have the time and expertise to conduct pre- and post-test counseling for genetic testing. A genetic counselor can provide pre- and post-test counseling, as well as educate the patient and family about genetics and inheritance. Genetic counselors can also collect pedigree and medical information[90,91].

FUTURE DIRECTIONS

The advent of massively parallel DNA sequencing (also known as "next-generation" DNA sequencing) provides clinicians and researchers with the ability to sequence entire genomes or entire coding regions of genomes (also known as "exomes"). This opportunity also presents a challenge: the interpretation of DNA sequence variants of unknown pathogenicity. In the absence of conclusive genetic evidence linking mutations of genes other than *SLC26A4* to EVA, direct Sanger di-deoxy sequencing of *SLC26A4* currently remains the most efficient and reliable routine diagnostic test for the etiology of EVA. In the future, research should be directed toward identifying or confirming other genetic causes of EVA. Another avenue of research is to identify the etiologic, probably genetic, co-factors that cause EVA in patients with one detectable mutant allele of *SLC26A4*.

CONCLUSION

Genetic testing for *SLC26A4* mutations in patients with hearing loss associated with EVA can provide useful information for establishing the etiology of the hearing loss, prognosis, clinical surveillance and management of the thyroid gland, and counseling families about the probability of EVA in one or both ears and severity of hearing loss in siblings of patients with EVA. The most informative aspect of an *SLC26A4* genotype is the number of mutant alleles, since this shows the strongest correlation with the severity of hearing loss, laterality (unilateral *vs* bilateral) of EVA, thyroid gland volume, and recurrence probability. Patients with two mutant alleles of *SLC26A4* typically have bilateral EVA, more severe hearing loss, a thyroid iodide organification defect associated with increased thyroid gland volume, and a 25% recurrence probability of EVA for each sibling. Patients with one mutant allele have unilateral or bilateral EVA, less severe hearing loss, on average, in the ear(s) with EVA, a normal thyroid gland, and a recurrence probability that is similar to that of patients with two mutant alleles. Patients with no mutations of *SLC26A4* have thyroid and auditory phenotypes that are indistinguishable from those in patients with one mutant allele, but the probability of EVA in their siblings is much lower. Therefore even a "negative" *SLC26A4* mutation test result can provide useful diagnostic, prognostic, and familial recurrence information.

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BRIEF ARTICLE

Surface electromyography for diagnosing dysphagia in patients with cerebral palsy

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Abstract

AIM: To determine the accuracy of 2-channel surface electromyography (sEMG) for diagnosing oropharyngeal dysphagia (OPD) in patients with cerebral palsy.

METHODS: Participants with cerebral palsy and OPD between 5 and 30 years of age and age- and sex-matched healthy individuals received sEMG testing during swallowing. Electrodes were placed over the submental and infrahyoid muscles, and sEMG recordings were made during stepwise (starting at 3 mL) determination of maximum swallowing volume. Outcome measures included submental muscle group maximum amplitude, infrahyoid muscle group maximum amplitude (IMGMA), time lag between the peak amplitudes of 2 muscle groups, and amplitude difference between the 2 muscle groups.

RESULTS: A total of 20 participants with cerebral palsy and OPD (OPD group) and 60 age- and sex-matched healthy volunteers (control group) were recruited. Among 20 patients with OPD, 19 had Dysphagia Outcome and Severity Scale records. Of them, 8 were classified as severe dysphagia (level 1), 1 was moderate dysphagia (level 3), 4 were mild to moderate dysphagia (level 4), 3 were mild dysphagia (level 5), and 3 were within functional limits (level 6). Although the groups were matched for age and sex, participants in the OPD group were significantly shorter, weighed less and had lower body mass index than their counterparts in the control group (both, $P < 0.001$). All sEMG parameter values were significantly higher in the OPD group compared with the control group ($P < 0.05$). Differences were most pronounced at the 3 mL swallowing volume. IMGMA at the 3 mL volume was the best predictor of OPD with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 85.0%, 90.0%, 73.9%, 94.7% and 88.8%, respectively.

CONCLUSION: Two-channel sEMG may be useful in the diagnosis of OPD in patients with cerebral palsy.

Key words: Cerebral palsy; Dysphagia; Surface electromyography; Maximum swallowing volume

Core tip: Surface electromyography (sEMG) parameters obtained using 2-channel recordings of submental and infrahyoid muscle activity differ significantly during swallowing between patients with oropharyngeal dysphagia (OPD) and cerebral palsy and healthy control individuals. These findings suggest that with further optimization and testing, 2-channel sEMG may be useful for the diagnosis of OPD in patients with cerebral palsy, as well as patients with other disorders.

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INTRODUCTION

Oropharyngeal dysphagia (OPD), defined as difficulty in the oral and/or pharyngeal phases of swallowing, which includes tolerance of secretions/saliva control and food/liquid, is a relatively common clinical condition that can have serious consequences[1]. OPD may result in inadequate food intake, which can result in malnutrition, dehydration, and decreased quality of life[2]. In addition, a common and potentially serious complication of OPD is aspiration pneumonia[3,4]. Unsurprisingly, OPD is associated with increased morbidity and mortality[2]. The incidence of OPD increases with age, and is particularly common in patients with neurologic disorders[1,5,6] including cerebral palsy[7]. The prevalence of OPD in children with cerebral palsy is estimated to be between 19% and 99%, and OPD can impact children's growth, nutrition and overall health[8,9]. Early diagnosis of OPD is essential for the prompt initiation of therapy to lower the risk of complications[9].

The current gold standard for diagnosing OPD is video fluoroscopic study of swallowing (VFSS). Despite the accuracy of VFSS, this approach has several limitations including exposure to radiation, high cost, and the need for specialized equipment and trained personnel[10]. Thus, the availability of a simple, fast, and low cost means of diagnosing OPD would be of significant benefit.

Surface electromyography (sEMG) has been used to assess the involvement of individual muscles in swallowing[11-15]. Gupta *et al*[16] first outlined the potential use of sEMG for the diagnosis of OPD. Crary *et al*[17] reported a strong degree of accuracy in identification of swallows *vs* non-swallow movements from sEMG traces and concluded that the sEMG graphic record is a valid and reliable tool for identifying normal swallows. In another study by Crary *et al*[18] the authors evaluated healthy adults with simultaneous videofluoroscopy and sEMG while swallowing 5 mL of liquid barium sulfate and found that swallow onset in the sEMG signal preceded the onset of all biomechanical events, and all biomechanical events demonstrated a strong correspondence to the sEMG signal with the strongest relationship between hyoid elevation-anterior displacement and the sEMG signal. These results suggest that because the sEMG signal is a useful indicator of major biomechanical events in the swallow, it can be used as the tool for investigating OPD. Vaiman *et al*[10,19] have been strong advocates of the use of sEMG in the screening of swallowing disorders including OPD, and have published evidence suggesting that 4-channel sEMG may be an effective means of screening for OPD in certain patient populations.

To our knowledge, however, no study has examined the use of sEMG for diagnosing OPD in patients with cerebral palsy. As OPD is relatively common in patients with cerebral palsy, the applicability of sEMG for diagnosing OPD in this patient population warrants investigation. Thus, the aim of this study was to determine the clinical feasibility and accuracy of using 2-channel sEMG for diagnosing OPD in patients with cerebral palsy.

MATERIALS AND METHODS

Participants

Participants with spastic bilateral cerebral palsy between 5 and 30 years of age and OPD who exhibited coughing during mealtime were recruited from the rehabilitation department clinic of the Maria Social Welfare Foundation of Taiwan. In all patients, OPD was diagnosed by videofluoroscopy within 1 mo of sEMG testing. In brief, videofluoroscopy was performed with the patient in the upright (sitting) position and lateral and/or posteroanterior views were obtained. Swallowing was evaluated by simultaneous video and audio recording, and the agents used were thin liquid barium, thick liquid barium, puree barium, paste barium, and solid barium cookie. The caregiver was instructed to feed the thin liquid to the patient in volumes of 2, 5, and 10 mL *via* spoon-feeding (or through a straw or directly from a cup if patient is able). Thick liquid, puree, and paste were fed in volumes of 2, 5, and 10 mL *via* spoon. The barium cookie was divided into 2 cm^2 sized pieces and fed with a small amount of paste barium.

Age- and sex-matched healthy volunteers were recruited from the general public as a control group. Individuals who had skin diseases or wounds located where the electrodes would be attached were excluded. This study was approved by the Institutional Review Board of Cheng-Ching Hospital, Taichung, Taiwan. All participants provided written informed consent before the commencement of any study-related procedures. For participants unable to provide consent or under the age of 18, consent was obtained from a parent or legal guardian.

Dysphagia outcome and severity scale

The severity of OPD was assessed in each participant using the Dysphagia Outcome and Severity Scale (DOSS)[20], which classifies dysphagia as follows: level 7 = normal; level 6 = within functional limits; level 5 = mild dysphagia; level 4 = mild to moderate dysphagia; level 3 = moderate dysphagia; level 2 = moderate to severe dysphagia; and level 1 = severe dysphagia. The DOSS was scored according to the results of videofluoroscopy and was representative of the videofluoroscopic evaluation.

sEMG examination

A 2-channel sEMG device (Bagnoli™ Handheld EMG System, Delsys Inc., Boston, MA) was used for examinations. Electrodes were placed on the skin over the submental (0.5 cm above the hyoid, parallel to, and right of the midline) and infrahyoid (0.5 cm below the hyoid, parallel to, and right of the midline) muscles as described

by Vaiman[19] to record changes in sEMG potential when different volumes of water were swallowed. sEMG signals were amplified (1000 ×) and filtered (wide band: 20-450 Hz), and root mean square values were used for analysis. Parameters measured included submental muscle group maximum amplitude (SMGMA), infrahyoid muscle group maximum amplitude (IMGMA), the time lag between the peak amplitudes of 2 muscle groups (TDBMG), and the amplitude difference between the 2 muscle groups (ADBMG). Sample volumes of water for testing were based on amounts used by Ozdemirkiran *et al*[21]. Testing began at 3 mL, followed by 5, 8, 12, and 15 mL. Thereafter, 5 mL was added to each successfully swallowed volume until the participant could not ingest the new volume in a single swallow. If a participant could not ingest the initial 3 mL of water in a single swallow, the volume was reduced to 2 or 1 mL as necessary. The maximum volume of water that each participant was able to ingest in a single swallow, the maximum swallowing volume (MSV), was recorded.

Statistical analysis

Continuous variables are presented as mean ± SD, unless otherwise indicated, whereas categorical variables are presented as frequencies with percentages. Demographic variables were compared between groups by independent samples *t*-test (continuous variables) or χ^2 test (categorical variables). After adjusting for body mass index (BMI), sEMG parameters were compared between groups using analysis of covariance. The relationships between DOSS score and different sEMG parameters were determined by calculating Spearman's partial correlation coefficients after adjusting for BMI. Standard measures of test validity including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for each sEMG parameter. Receiver operating characteristic (ROC) curves, plots of 1-specificity *vs* sensitivity for all cutoff values over the range of values for each sEMG parameter, were constructed to examine the diagnostic performance of different sEMG parameters. The optimal cutoff values for sEMG parameters to distinguish the experimental group from the control group were determined using the maximized Youden index, defined as sensitivity + specificity-1. A univariate logistic regression model was constructed with the OPD group as the binary dependent variable (1 = dysphagia, 0 = control), and the sEMG parameters as the continuous variable. The *c* statistic from the logistic regression model corresponds to the area under the ROC curve (AUC). An AUC of 0.5 indicates that the variable does not provide a better than chance prediction of OPD. A test of the null hypothesis that the AUC was 0.5 was performed using the Wilcoxon rank sum test. Comparisons between AUCs for different sEMG parameters were conducted using a previously described method[22]. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC). A two-tailed $P < 0.05$ indicated statistical significance.

Table 1 Demographic characteristics of participants in the oropharyngeal dysphagia and control groups *n* (%)

Characteristic	OPD group[1] (*n* = 20)	Control group[2] (*n* = 60)	*P* value
Sex			
Male	14 (70.0)	42 (70.0)	1.000[3]
Female	6 (30.0)	18 (30.0)	
Age (yr)	14.5 ± 6.2	14.5 ± 6.1	0.998[4]
Height (cm)	128.1 ± 19.2	153.4 ± 20.1	< 0.001[4]
Weight (kg)	25.4 ± 12.7	47.7 ± 17.6	< 0.001[4]
BMI (kg/m^2)	14.6 ± 3.4	19.5 ± 3.5	< 0.001[4]
DOSS[6]			
Level 1	8 (42.1)	0 (0.0)	< 0.001[5]
Level 2	0 (0.0)	0 (0.0)	
Level 3	1 (5.3)	0 (0.0)	
Level 4	4 (21.1)	0 (0.0)	
Level 5	3 (15.8)	0 (0.0)	
Level 6	3 (15.8)	0 (0.0)	
Level 7	0 (0.0)	60 (100.0)	

Data are presented as mean ± SD. [1]Participants in the dysphagia group had cerebral palsy; [2]Participants in the control group did not have cerebral palsy and were healthy; [3]Determined by χ^2 test; [4]Determined by independent samples *t*-test; [5]Determined by Fisher's exact test; [6]Dysphagia outcome and severity scale (DOSS) score was missing for one oropharyngeal dysphagia (OPD) patient. BMI: Body mass index. Level 7 = normal; Level 6 = within functional limits; Level 5 = mild dysphagia; Level 4 = mild to moderate dysphagia; Level 3 = moderate dysphagia; Level 2 = moderate to severe dysphagia; Level 1 = severe dysphagia.

RESULTS

Demographic characteristics

A total of 20 participants with cerebral palsy and OPD (OPD group) and 60 age- and sex-matched healthy volunteers (control group) were recruited. Among 20 patients with OPD, 19 had DOSS records. Of them, 8 were classified as severe dysphagia (level 1), 1 as moderate dysphagia (level 3), 4 as mild to moderate dysphagia (level 4), 3 as mild dysphagia (level 5), and 3 were within functional limits (level 6). Although the groups were matched for age and sex, participants in the OPD group were significantly shorter, weighed less and had lower BMI than their counterparts in the control group (both, $P < 0.001$, Table 1).

MSV and sEMG parameters

After adjusting for BMI, the MSV was significantly lower, and all sEMG parameters were significantly higher, in the OPD group compared with the control group (all, $P < 0.05$, Table 2). Although there were significant between group differences for all sEMG parameters at the 3 mL swallowing volume and at the MSV, the between group differences were more pronounced at the 3 mL swallowing volume.

Correlations between DOSS score and sEMG parameters

After adjusting for BMI, DOSS score was negatively correlated with all sEMG parameters (Table 3). The correlations were significant for SMGMA, IMGMA, and ADBMG at the 3 mL swallowing volume (all, $P < 0.05$). None of the sEMG correlations at the MSV were significant.

Table 2 Surface electromyographic findings for participants in the oropharyngeal dysphagia and control groups after adjusting for body mass index

Characteristic	OPD group (n = 20)	Control group (n = 60)	β[1] (SE)	P value
MSV (mL)	3.70 ± 3.01	54.50 ± 24.47	-33.87 (5.32)	< 0.001
At 3 mL swallowing volume				
SMGMA (μV)	80.77 ± 65.00	35.02 ± 13.02	38.30 (10.21)	< 0.001
IMGMA (μV)	88.89 ± 78.52	30.23 ± 10.55	44.09 (11.68)	< 0.001
TDBMG (s)	0.35 ± 0.35	0.13 ± 0.12	0.22 (0.06)	< 0.001
ADBMG (μV)	60.59 ± 71.50	10.18 ± 11.49	38.55 (10.84)	< 0.001
At MSV				
SMGMA (μV)	100.24 ± 96.96	52.78 ± 28.05	34.90 (16.10)	0.033
IMGMA (μV)	98.28 ± 89.75	51.32 ± 21.78	30.59 (14.20)	0.034
TDBMG (s)	0.35 ± 0.35	0.15 ± 0.15	0.20 (0.07)	0.004
ADBMG (μV)	62.87 ± 73.05	18.75 ± 22.00	33.92 (12.20)	0.007

Data are presented as mean ± SD unless otherwise indicated. [1]Mean difference between experimental and control group adjusted for body mass index (BMI). MSV: Maximum swallowing volume; SMGMA: Submental muscle group maximum amplitude; IMGMA: Infrahyoid muscle group maximum amplitude; TDBMG: Time difference between 2 muscle groups; ADBMG: Amplitude difference between 2 muscle groups; OPD: Oropharyngeal dysphagia.

Table 3 Spearman's partial correlations between Dysphagia Outcome and Severity Scale score and surface electromyographic findings after adjusting for body mass index (n = 79[1])

Characteristic	Correlation coefficient	P value
At 3 mL swallowing volume		
SMGMA (μV)	-0.329	0.003
IMGMA (μV)	-0.389	< 0.001
TDBMG (s)	-0.153	0.182
ADBMG (μV)	-0.353	0.002
At MSV		
SMGMA (μV)	-0.117	0.309
IMGMA (μV)	-0.056	0.626
TDBMG (s)	-0.168	0.140
ADBMG (μV)	-0.193	0.091

[1]One patient with a missing Dysphagia Outcome and Severity Scale score value was omitted from this analysis. MSV: Maximum swallowing volume; SMGMA: Submental muscle group maximum amplitude; IMGMA: Infrahyoid muscle group maximum amplitude; TDBMG: Time difference between 2 muscle groups; ADBMG: Amplitude difference between 2 muscle groups.

Diagnostic performance of sEMG parameters

The sEMG parameters at the 3 mL swallowing volume were better predictors of OPD than the sEMG parameters at the MSV (Table 4). The AUCs for IMGMA and ADBMG at the 3 mL swallowing volume were significantly higher than the AUCs for SMGMA, IMGMA, and ADBMG at the MSV ($P < 0.05$). Similarly, the AUC for SMGMA at the 3 mL swallowing volume was significantly higher than the AUC for SMGMA at the MSV ($P = 0.001$). Of the sEMG parameters at the 3 mL swallowing volume, IMGMA was the best predictor of OPD, followed by SMGMA. At the MSV, SMGMA and IMGMA were poor (no better than chance alone) predictors of OPD. Because sEMG parameters at the 3 mL swallowing volume showed better diagnostic performance for detecting OPD than those at the MSV did, the effectiveness of various combinations of these 4 parameters to detect OPD was further analyzed. Since TDBMG exhibited the lowest diagnostic performance (AUC = 0.723) among these 4 parameters, 3 scenarios were investigated as follows: (1) Of 4 parameters, at least 2 parameters met diagnostic criteria (≥ cutoff value); (2) Of 4 parameters, at least 3 parameters met diagnostic criteria; and (3) Of 3 parameters other than TDBMG, at least 2 parameters met diagnostic criteria. The diagnostic performances of these 3 scenarios are shown in Table 5.

DISCUSSION

Our study is the first to compare sEMG parameters obtained using a 2-channel surface electromyograph during swallowing between patients with cerebral palsy and OPD and healthy control individuals. We found that there were marked between group differences for all sEMG parameters at the 3 mL swallowing volume and the MSV. Specifically, all sEMG parameters were significantly higher in the OPD group compared with the control group. Further analyses indicated that sEMG parameters at the 3 mL swallowing volume, in particular IMGMA, were the best predictors of OPD. The DOSS used in this study has been shown to exhibit high inter-rater (90%) and intra-rater (93%) agreement[20] and has been used in the evaluation of infants with Apert syndrome[23].

Our finding that sEMG parameters were significantly different during swallowing between patients with OPD and cerebral palsy and healthy control individuals is consistent with the finding of Vaiman *et al*[10] that there are differences in sEMG between patients with various diseases and conditions including OPD, tonsillitis, and salivary gland disease and normal healthy individuals, and those of Crary *et al*[17] who have reported that sEMG can reliably identify normal swallows and that sEMG signals are strongly correlated with the biomechanical events of swallowing[18]. Our findings also support the assertion of Vaiman *et al*[10] that sEMG is a viable screening method for OPD. Different than in the studies by Vaiman *et al*[10,19] in which a 4-channel sEMG was used, we used a 2-channel sEMG and found this to be adequate for detecting between group differences. Compared to 4-channel sEMG, 2-channel sEMG is less expensive and more accessible. The 2-channel system makes sEMG examinations on patients who cannot cooperate for a long period of time easier, thus making it more practical in clinical settings. Various other non-invasive, swallowing-based means of screening for OPD have been described in the literature (Table 6), and the 2-channel sEMG for detecting OPD at the 3 mL swallowing volume in patients with cerebral palsy we have described compares favorably with the majority of previously reported approaches in terms of sensitivity, specificity, PPV, and NPV.

Importantly, we found that sEMG parameters measured during swallowing of a 3 mL volume were better

Table 4 Diagnostic performance of difference surface electromyographic parameters for detecting oropharyngeal dysphagia

Characteristic	AUC (95%CI)	*P* value	Optimal cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
At 3 mL swallowing volume								
SMGMA (μV)	0.80 (0.68-0.92)[1]	< 0.001	39.27	80.0	73.3	50.0	91.7	75.0
IMGMA (μV)	0.88 (0.78-0.98)[1,2,3]	< 0.001	37.30	85.0	90.0	73.9	94.7	88.8
TDBMG (s)	0.72 (0.59-0.86)	< 0.001	0.19	70.0	70.0	43.8	87.5	70.0
ADBMG (μV)	0.82 (0.71-0.93)[1,2,3]	< 0.001	12.02	75.0	76.7	51.7	90.2	76.3
At MSV								
SMGMA (μV)	0.63 (0.48-0.79)	0.091	110.00	40.0	98.3	88.9	83.1	83.8
IMGMA (μV)	0.64 (0.48-0.81)	0.097	79.55	45.0	90.0	60.0	83.1	78.8
TDBMG (s)	0.72 (0.59-0.84)	< 0.001	0.19	70.0	70.0	43.8	87.5	70.0
ADBMG (μV)	0.70 (0.56-0.84)	0.005	35.69	50.0	90.0	62.5	84.4	80.0

[1]Area under receiver operating characteristic curve (AUC) significantly higher compared with submental muscle group maximum amplitude (SMGMA) at maximum swallowing volume (MSV) ($P < 0.01$, *vs* SMGMA at MSV); [2]AUC significantly higher compared with infrahyoid muscle group maximum amplitude (IMGMA) at MSV ($P < 0.05$, *vs* IMGMA at MSV); [3]AUC significantly higher compared with amplitude difference between 2 muscle groups (ADBMG) at MSV ($P < 0.01$, *vs* ADBMG at MSV). PPV: Positive predictive value; NA: Not applicable; NPV: Negative predictive value; TDBMG: Time difference between 2 muscle groups.

Table 5 Diagnostic performance of combinations of surface electromyography parameters at the 3 mL swallowing volume for detecting oropharyngeal dysphagia

sEMG parameters at the 3 mL swallowing volume	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Of 4 parameters					
≥ 2 parameters met diagnostic criteria[1]	100	71.7	54.1	100	78.8
≥ 3 parameters met diagnostic criteria[1]	85.0	93.3	81.0	94.9	91.3
Of 3 parameters other than TDBMG					
≥ 2 parameters met diagnostic criteria[1]	95.0	75.0	55.9	97.8	80.0

[1]Diagnostic criteria of each surface electromyography (sEMG) parameter at the 3 mL are as follows: submental muscle group maximum amplitude (SMGMA) ≥ 39.27 μV; infrahyoid muscle group maximum amplitude (IMGMA) ≥ 37.30 μV; time difference between 2 muscle groups (TDBMG) ≥ 0.19 s; amplitude difference between 2 muscle groups (ADBMG) ≥ 12.02 μV. AUC: Area under receiver operating characteristic curve; PPV: Positive predictive value; NA: Not applicable; NPV: Negative predictive value; MSV: Maximum swallowing volume.

Table 6 Summary of studies of non-invasive screening methods for oropharyngeal dysphagia

Ref.	Test	No. of participants	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
DePippo *et al*[24]	Burke Dysphagia Screening Test	44	76	59	-	-
Gottlieb *et al*[25]	50 mL Drinking Test	180	80	86	-	-
Ellul *et al*[26]	Standardized Swallowing Assessment	136	68	86	50	88
Smithard *et al*[27]	Bedside Swallowing Assessment	83	70	66	50	85
Hinds *et al*[28]	Timed Test	115	73	67	-	-
Mari *et al*[29]	3oz Water Swallow Test	93	74	74	71	77
Smith *et al*[30]	Pulse Oximetry	53	86	-	69	
Martino *et al*[31]	Toronto Bedside Swallowing Screening Test	115	82	39	24	90
Kopey *et al*[32]	3-Sp Test	223	21	99	88	72
Antonios *et al*[33]	Modified Mann Assessment of Swallowing Ability	150	93	86	79	95

PPV: Positive predictive value; NPV: Negative predictive value.

predictors of OPD than those measured during MSV, and that IMGMA was the best diagnostic predictor at the 3 mL swallowing volume, as indicated by relatively high sensitivity, specificity, PPV, NPV, and accuracy. It is interesting to postulate why sEMG is more sensitive at predicting OPD at a volume of 3 mL than at MSV. Crary *et al*[34] used sEMG to evaluate the patients with OPD secondary to brainstem stroke and compared the results with those of age- and sex-matched controls. The results showed that patients with OPD secondary to brainstem stroke differed in both amplitude and timing aspects of swallowing attempts from asymptomatic controls. Specifically, during swallow attempts dysphagic patients produced more muscle activity over a shorter duration and with less coordination. Peak microvolt values (max amplitude) during the swallowing attempts represent the maximum myoelectric activity observed during swallowing, and the brains that have experienced stroke produced

more muscle activity due to poor coordination. Similarly, our findings showed that the maximum amplitude of the patients with dysphagia secondary to cerebral palsy differed from the age-matched controls. Presumably the patients with OPD and cerebral palsy produce more muscle activity as a result of poor coordination than healthy individuals. For healthy individuals it is relatively easy to swallow a small volume (3 mL), whereas a larger volume is more difficult. In the individuals with OPD and cerebral palsy, the difficulty occurs at even small volumes.

We believe the approach for diagnosing OPD described herein offers several advantages over other diagnostic options. First, the examination is relatively quick because only 2 electrodes need to be attached to the patient. Second, only a small volume of fluid (3 mL) is required to be swallowed for optimal testing. Third, because only 3 mL of fluid is used, the risk of choking is reduced. Fourth, the test is non-invasive and avoids radiation exposure that is unavoidable with VFSS. Finally, this is a low cost procedure that requires minimal training and can be conducted in the absence of a speech therapy specialist. Given the aforementioned benefits, sEMG may be used as a simple screening assessment to initiate referral to speech therapy for more extensive evaluation and management.

There are several limitations to this study that warrant acknowledgement. First, all participants in the OPD group had cerebral palsy; thus, the findings may only be applicable to individuals with OPD and cerebral palsy. Nevertheless, we feel our findings are still important because OPD is a common comorbidity in patients with cerebral palsy, particularly in children with severe cerebral palsy[7]. Second, control participants were healthy individuals. A more appropriate control group in this context would have been patients with cerebral palsy, but not OPD. This was not part of the study design due to ethical concerns. Having patients with cerebral palsy, of whom most are children, with no swallowing problems endure the lengthy and intensive evaluation from which they would gain no benefit would bring unnecessary hardship and distress to these patients. A third limitation is the relatively small number of participants in the OPD group. Lastly, because of the small number of patients subgroup analysis could not be performed.

In conclusion, we have found that sEMG parameters differ significantly during swallowing between patients with OPD and cerebral palsy and healthy control individuals. Notably, these findings were obtained using 2-channel recordings of submental and infrahyoid muscle activity. Our findings lead us to suggest that, with further optimization and testing, 2-channel sEMG may be useful for the diagnosis of OPD in patients with cerebral palsy, and indeed other patients.

COMMENTS

Background

Oropharyngeal dysphagia (OPD) may result in inadequate food intake, which can result in malnutrition, dehydration, and decreased quality of life. In addition, aspiration pneumonia is a common and potentially serious complication. The incidence of OPD increases with age, and is particularly common in patients with neurologic disorders, including cerebral palsy. The current gold standard for diagnosing OPD is video fluoroscopic study of swallowing (VFSS); however, has several limitations including exposure to radiation, high cost, and the need for specialized equipment and trained personnel. Thus, the availability of a simple, fast, and low cost means of diagnosing OPD would be of significant benefit.

Research frontiers

Surface electromyography (sEMG) has been used to assess the involvement of individual muscles in swallowing. As OPD is relatively common in patients with cerebral palsy, the applicability of sEMG for diagnosing OPD in this patient population warrants investigation.

Innovations and breakthroughs

This study is the first to compare sEMG parameters obtained using a 2-channel surface electromyograph during swallowing between patients with cerebral palsy and OPD and healthy control individuals. The authors found that there were marked between group differences for all sEMG parameters at the 3 mL swallowing volume and the maximum swallowing volume. Specifically, all sEMG parameters were significantly higher in the OPD group compared with the control group. Further analyses indicated that sEMG parameters at the 3 mL swallowing volume, in particular infrahyoid muscle group maximum amplitude, were the best predictors of OPD.

Applications

Although these results indicate that the diagnostic performance of sEMG is not good enough to replace the VFSS, sEMG can be considered as an initial screening tool due to its non-invasive nature and low cost. As the first clinical study to apply sEMG for detecting OPD in cerebral palsy, the authors believe the results demonstrate the feasibility of using sEMG as a screening method and can be a reference for further investigation of the method in patients with cerebral palsy.

Terminology

OPD is defined as difficulty in the oral and/or pharyngeal phases of swallowing, which includes tolerance of secretions/saliva control and food/liquid, is a relatively common clinical condition that can have serious consequences. For a VFSS, the patient swallows hard and/or soft foods and liquids that are mixed with barium. Fluoroscopy of the swallowing function is performed. sEMG uses electrode placed on the skin to detect the electrical potential generated by muscle cells when these cells are electrically or neurologically activated.

Peer review

In this paper the authors evaluate sEMG as a new helpful tool for the screening and early diagnosis of dysphagia in patients with cerebral palsy: the conclusion of the authors is that sEMG may be useful in the diagnosis of OPD. Evaluation of OPD due to brainstem stroke by sEMG was already reported, but this paper is the first to assess sEMG as a screening tool in cerebral palsy. The paper is well presented and written in a well English.

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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases.

Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

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Italics

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