Auditory and Otologic Phenotypic Manifestations in Alström Syndrome

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Abstract

Here we report the audiological and clinical findings for 37 patients (20 females, 17 males) with Alström syndrome, aged 1.6-38 years. Age of hearing loss identification ranged from 1.5-15 years, and for those with known newborn hearing screening results, 14 passed and 1 did not. Cross sectional analysis showed progression of pure-tone average at a rate of 10-15 dB/decade. Otoacoustic emissions (OAEs), acoustic reflexes, and word recognition abilities were commensurate with degree of hearing loss. Auditory brainstem responses (ABR) were remarkably robust, and latencies were normal or consistent with the degree of hearing loss for all but three patients with interpeak latency prolongations. Overall hearing loss was predominantly symmetric, progressive, and sensorineural. These novel and comprehensive data provide overwhelming evidence for cochlear dysfunction, although infrequent concomitant retrocochlear involvement remains a consideration.

Introduction

Alström syndrome is a rare ciliopathy caused by mutations in ALMS1 that encodes a ciliary protein. Clinically it is characterized by severe vision loss over the first 2 decades of life secondary to atypical retinal degeneration, postlingual progressive sensorineural hearing loss (SNHL), childhood-onset diabetes, diabetes due to insulin resistance, hyperlipidemia, hepatorenal, and pulmonary disease, and normal intelligence. Glue ear during childhood and chronic otitis media (OM) as late as the third decade of life are common, and overall incidence of otitis media is 42% (Marshall et al, 2005).

ALMS1 has localized to the basal bodies of hair cells and supporting cells in the neonatal rat organ of Corti. Alms1 disrupted mice have shown abnormalities of the shape and orientation of stereociliary bundles and adult animals have loss of outer hair cells and progressive appearance of large lesions in the stria vascularis (Jagger et al, 2013). While progressive decline in pure tone sensitivity has been documented in humans, the audiography profile for Alström syndrome has not been fully characterized. OAEs and ABR evaluations, which are critical assessments for description of sensory versus neural hearing loss, have not been reported in a cohort of this size (Bahmad et al, 2014).

Methods

Participants

Thirteen patients (17 males and 20 females) with Alström syndrome, aged 1.6-38 years (mean±SD=16.14, SD=10.59) participated in comprehensive audiological and clinical evaluation at the NIH Clinical Center between February 2013 and June 2014.

Test Procedures

Behavioral evaluations comprised age- and ability-appropriate audiological evaluations including air- and bone-conduction pure-tone thresholds, speech thresholds, and evaluation of word recognition ability in quiet (SQ-61). Middle ear function was assessed using 226 Hz tympanometry and determination of ipsilateral and contralateral acoustic reflex thresholds (GSI-Tympan). Distortion product otoacoustic emissions (DPOAEs) were evaluated in quieter octave bands over the frequency range 842-7966 Hz (OtoDynamics LO88). ABRs were recorded to condensation and rarefaction, air-conducted, broadband clicks delivered via insert earphones at 85/95 dB nHL at rates of 8.3 and 63.3/sec, and at 55/65 dB nHL at 8.3/sec (GSI Audera). Otoacoustic emissions (OAEs) and ABRs, which are critical assessments for description of sensory versus neural hearing loss, have not been reported in a cohort of this size (Bahmad et al, 2014).

Objective:

To expand and comprehensively characterize the auditory and otologic manifestations of persons with Alström syndrome.

Data Interpretation and Analysis

Pure tone thresholds were categorized as within normal limits (WNL) when ≤20 dB HL, mildly reduced when ≥20-40 dB HL, moderately reduced when ≥40-70 dB HL, severely reduced when ≥70-90 dB HL and profoundly reduced when >90 dB HL. Overall degree of hearing loss was based on a four frequency pure-tone average (4F-PTA; 0.5/1/2/4kHz) or the speech threshold when pure tone data could not be obtained (n=2). Type of hearing loss was based on the difference between the air- and bone-conduction threshold for each frequency to determine the degree of hearing loss (Marshall et al, 2011). Word recognition scores were evaluated as percentage correct or proportionate using ranges established by Dubno et al. (1995). Peak static compliance, ear canal volume, and middle ear pressure were interpreted as WNL/low, WNL/small/large, and WNL/negative/positive, respectively, using age-appropriate norms (Margolis and Heller, 1987). The data were presented as type A, B, C per Jerger (1970). Acoustic reflex thresholds were interpreted in light of pure tone thresholds using normative data from Gelfand et al. (1989).

Descriptive and inferential statistics were computed using Microsoft Excel (v14.3.6) and Prism GraphPad (v6.0f).

Discussion/Conclusions

• Despite a history of recurrent middle ear disease during childhood, 79% of our participants had normal tympanometry, 3/74 ears had a mixed hearing loss, and none had conductive hearing loss at the time of NIH evaluation. The predisposition for recurrent OM lessens as they get older.

• The hearing loss associated with Alström syndrome is predominantly symmetric, sensorineural, and plateaus at a moderate to severe degree (Fig 3 and Table 2). Progression of the hearing loss occurs at a rate of ~10-15 dB/decade (Fig 6) and is similar across the audiometric frequency range. Additionally, word recognition scores are proportional to degree of hearing loss. Of note, these patients benefit from amplification and if necessary, cochlear implantation (Florence et al, 2010).

• The combination of test findings on pure tone audiometry, DPOAEs and ABRs points to an outer hair cell and/or stria vascularis site of lesion, consistent with that observed in the animal model. However, abnormal ABR findings observed in 4 patients (6 ears) could not be explained by the degree of hearing loss.

• Osteosclerosis of the superior semicircular canal, a hallmark feature of Alström syndrome, was not observed in this cohort.

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