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Audiologic and Vestibular Findings in Wolfram Syndrome

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Abstract

Context—Clinical manifestations of Wolfram syndrome (WS), a rare autosomal recessive neurodegenerative disease, include diabetes mellitus (DM), optic nerve atrophy (OA), diabetes insipidus (DI) and sensorineural hearing loss (SNHL).

Objective—Assessment of auditory and vestibular function in WS patients using a standardized protocol.

Design—Prospective cohort study of 11 patients using otoscopic inspection, tympanometry, otoacoustic emissions, pure tones, speech in noise, the speech intelligibility index and rotational chair testing.

Results—Mean SNHL diagnosis was 7.3 years with 55% prevalence. Four patients with a Speech Intelligibility Index (SII) less than 0.75 (better ear) routinely used bilateral amplification devices. Two patients with normal hearing sensitivity exhibited abnormal speech in noise (SIN) scores. The only patient with significant vestibular dysfunction also had a distinctive low frequency component to her SNHL.

Conclusions—Hearing loss may occur earlier than previously suspected and comprehensive testing including speech in noise testing may reveal deficits not apparent with pure tone testing. Particular configurations of hearing loss may indicate a need for comprehensive vestibular assessment. Because SNHL can be the first symptom of WS, audiologists and otolaryngologists should be vigilant about referring patients with hearing loss for ophthalmologic examination.

Keywords

Wolfram syndrome; vestibular function; hearing loss; speech intelligibility index

INTRODUCTION

Wolfram syndrome (WS) is an autosomal recessive neurodegenerative disease with an estimated prevalence varying worldwide from one in 68,000 to one in 770,000 (Barrett & Bunday 1997; Kumar 2010). Clinical manifestations include diabetes mellitus (DM), optic nerve atrophy (OA), diabetes insipidus (DI), sensorineural hearing loss (SNHL), neurological symptoms, renal tract abnormalities, psychiatric disorders and gonadal disorders. The disease is fatal with death usually occurring before 50 years of age (Barrett & Bunday 1997).

Hearing loss of some degree is observed in at least 62% to 72% of patients with WS (Higashi 1991; Kumar 2010). The most commonly reported presentation of hearing loss in WS is a high-frequency SNHL that is typically diagnosed during the second or third decade of life (see Table, Supplemental Digital Content 1, which provides data and references from series and case reports). However, with notable exceptions (Pennings et al 2004; Plantinga et al 2008; Hilson et al 2009), the majority of published reports do not include sufficient details about the audiologic measures used to specify the severity or progression of hearing loss in WS. Because there are very few reports of vestibular function in patients with WS and even fewer in which both auditory and vestibular function are measured, the relationship between balance and auditory function remains uncertain.

The intent of this study was to assess auditory and vestibular function in an international cohort of patients with WS, using a fixed protocol of standardized tests. The test battery includes traditional tests of auditory and vestibular function, as well as audiologic tests that have not been reported previously in this clinical population, such as measures of distortion product otoacoustic emissions (DPOAEs), and speech-in-noise (SIN) as well as calculation of the speech intelligibility index (SII). The same protocol will be applied during yearly follow-up assessments of these patients and compared to the baseline measures reported here. Such a comparison will assist in determining the patterns and progression of hearing and vestibular loss in patients who have WS.

MATERIALS AND METHODS

Participants

Audiologic testing was administered to 11 patients (5.8 to 23.8 yr). Of the 11 patients, three (W03, W04 and W12) wore bilateral hearing aids and one (W05) had bilateral cochlear implants. Due to time constraints, three patients (W05, W07 and W13) were unable to participate in vestibular testing and limited audiologic assessment was conducted with W05. Three patients (W09, W10, and W11) were siblings. W07 had a first cousin and two distant cousins with WS who were not included in the cohort.

Procedures

Audiologic testing included otoscopic inspection, pure-tones (0.25 to 8 kHz), tympanometry, distortion product otoacoustic emissions (DPOAEs), unaided speech reception thresholds (SRTs) and unaided testing of speech in noise (SIN). Speech Intelligibility Index (SII) scores were calculated for each ear based on pure tone test results

in the unaided condition (ANSI S3.5-1997). Unaided assessment refers to testing completed without the use of hearing aids (W03, W04 and W12) or cochlear implants (W05).

Hearing sensitivity was considered abnormal if the air conduction (AC) pure tone average (PTA) of 0.50, 1 and 2 kHz was greater than 20 dB HL or 2 or more frequencies were greater than 20 dB HL. Bone conduction (BC) thresholds were assessed if the AC thresholds were greater than or equal to 20 dBHL. DPOAEs, which assess outer hair cell function in the cochlea, were measured and analyzed for 2, 3, and 4 kHz. Criterion for normal DPOAEs was greater than or equal to the 10th percentile (Gorga et al. 2005), that is -9.82 dB SPL at 2 kHz, -11.50 dB SPL at 3 kHz and -5.93 dB SPL at 4 kHz. with signal-to-noise ratio of greater than or equal to 6 dB.

SRTs were obtained with the CID W1 spondee word list via recorded test stimuli. SNR-50 scores for the BKB-SIN speech-in-noise test were considered normal if they fell within 2 SD of the mean using the following published criteria: 5-6 yr (m=3.5 dB, SD=2.0 dB); 7-10 yr (m=0.8 dB, SD=2.0 dB); 11-14 yr (m=-0.9 dB, SD=1.1 dB); adults (m=-2.5 dB, SD=0.8 dB) (Etymotic Research, Inc. 2005).

Vestibular testing consisted of stimuli presented at 0.025, 0.05, 0.25, and 0.5 Hz at a peak velocity of 60 deg/sec in a standard clinical rotary test chair. The same chair was used to measure responses to rotational impulses using velocity steps of 100 deg/sec acceleration.

Instrumentation

Testing was conducted in a sound-treated room (Industrial Acoustics Company, Inc.). Auditory stimuli were presented with the Madsen Orbiter-922 audiometer calibrated to American National Standards Institute (ANSI S3.6-1996) via sound field, insert earphones, or a bone conduction oscillator. Tympanometric measures were obtained with the Madsen Zodiac 901. DPOAE measures were obtained with the Interacoustics OtoRead with f1 set to 65 dB SPL and f2 set to 55 dB SPL. The SII was calculated on the Audioscan Verifit.

Vestibular testing was performed with a rotational chair (System 2000, Micromedical Technologies, Chatham, IL).

RESULTS

Fifty-five percent of the patients had SNHL. Mean age of diagnosis for SNHL was 7.3 yr for our cohort (see Table, Supplemental Digital Content 2, which shows age at diagnosis of SNHL relative to DM, DI and OA). In most cases the exact age of onset was unknown. Audiograms for four patients with SNHL are shown in Figure 1. Not shown are data for W05, who had profound bilateral hearing loss diagnosed at 20 months of age and has bilateral cochlear implants, W11, who exhibited slight-to-mild mixed hearing loss, with a transient conductive component, W07 who had a unilateral transient conductive loss, and those patients with normal bilateral hearing (W02, W09, W10, and W13). With the exception of W05, patients less than 15 years of age had PTAs less than 20 dB HL for the better ear, compared to PTAs of 28.3 to 58.3 dB HL for the better ear of patients greater than

15 years of age (see Table, Supplemental Digital Content 3, which shows PTA, high frequency average, hearing status, SII, and BKB-SIN results).

SII scores ranged from 0.0 (no speech cues audible) to 1.0 (all speech cues audible). Of the four patients with SII less than 0.75 for the better ear, W05 relies on bilateral cochlear implants and W03, W04, and W12 wear bilateral hearing aids. DPOAEs were reasonably consistent with pure tone thresholds (see Table, Supplemental Digital Content 4, which shows DPOAE data).

Unexpectedly, W10 and W13, who both had normal hearing sensitivity, produced abnormal BKB-SIN scores with an SNR-50 of 3.0 for W10 and 9.0 for W13, suggestive of difficulty listening in noise. Subsequent testing with speech in quiet at 40 dB SL re: SRT with CID W22 for W10 and Word Intelligibility by Picture Index (Ross & Lerman 1971) for W13 was normal with scores of 96% (both ears) for W10 and 94% (right ear) and 96% (left ear) for W13. As anticipated, patients with significant hearing loss (W03, W04 and W12) had SII less than 0.75 and abnormal SNR-50 scores on the BKB-SIN.

Results of sinusoidal vestibular and step velocity testing are shown in Figure 2. W04 had abnormally low gains and W02 and W09 had borderline low gains across frequencies tested. All patients had normal or near-normal phase leads with the exception of W04, whose low-frequency phase lead was pathologically elevated. On step velocity testing, W02, W09, and W04 all had borderline low gains in at least one direction and W04 had a markedly decreased time constant in both directions.

DISCUSSION

Although prevalence of SNHL (55%) in our cohort was consistent with existing reports, the average age at diagnosis of SNHL for our cohort was 7.3 years, which is younger than in most previous studies (Kumar, 2010; see Table, Supplemental Digital Content 1, which provides data and references from series and case reports). Plausible explanations include diagnostic criteria, the young age of the cohort and variable expression or penetrance. W05 and at least 10 previously reported patients had diagnosis of SNHL from birth to three years of age (see Table, Supplemental Digital Content 1, which provides data and references from series and case reports). Because SNHL can be the first symptom of WS, audiologists and otolaryngologists should recommend that patients are checked periodically for diabetes and vision conditions in young patients with SNHL.

According to previous studies, hearing loss is under-reported if it is based on patient or parent report rather than audiometric measures (Barrett & Bunday 1997; Simsek et al. 2003; Lombardo et al. 2005; Kumar 2010). In our cohort, no hearing difficulty was reported for W01 and W11; however, both were diagnosed with hearing loss based on pure-tone testing. Because the hearing loss in WS typically affects the high frequencies first and usually progresses slowly, age at diagnosis may be delayed by months or years relative to age of onset.

Although SNHL configurations were variable in our cohort, hearing loss was symmetrical, with all patients exhibiting high-frequency loss (Figure 1). Similar to Hansen et al. (2005),

conductive components were observed in two patients (W07 and W11). Subsequent testing of these patients indicated that the conductive components were transient.

The BKB-SIN was administered to represent auditory challenges based in everyday communication. Unexpectedly two normal hearing patients (W10 and W13) had abnormal BKB SIN scores. Factors that may have contributed include fatigue and reduced speech/language ability. It is also possible that the test is accurately portraying poorer SIN performance with this population. Follow-up speech testing with these patients is necessary to verify this finding.

With respect to treatment, Hilson et al. (2009) reported that hearing aid use was unsuccessful, but our data suggest otherwise. All four patients in our cohort with SII less than 0.75 use bilateral amplification devices. W03, W04, and W12 wear hearing aids and one W05 has cochlear implants. Although hearing benefit was not formally assessed, their routine use of the devices is a subjective indicator of benefit.

With respect to vestibular assessment, rotational chair testing indicated profound vestibular loss in W04, who was the oldest patient in the study (23.8 yr), although vestibular function was normal in W12, who was of the same approximate age. In addition to vestibular loss, W04 had a moderate-to-severe SNHL with an unusual audiometric configuration--significant low-frequency hearing loss as well as the more common high-frequency loss typical of WS. Of patients who received vestibular testing, W04 had the poorest PTA for both ears.

Our finding that profound bilateral vestibular loss was not common is typical of patients with WS (Higashi 1991; Pennings et al. 2004; Megighian and Savastano 2004). Hilson et al. (2009) reported temporal bone evidence for hair cell loss in the basal turn of the cochlea, typical of high-frequency hearing loss, but intact vestibular sense organs. Only one study has reported more vestibular dysfunction than hearing loss. Barjon et al. (1964) evaluated three patients and described bilateral vestibular loss both in a patient with a moderate SNHL across a wide range of frequencies (similar to findings for W04) and in a patient with essentially normal hearing. Overall, the findings of the present study and previous work suggest that vestibular loss may be more likely to occur in patients with a low-frequency component to their hearing loss.

Our study is limited because we did not include auditory brainstem response (ABR) testing. Systematic, longitudinal ABR data with a sufficient sample size are needed to determine the relationship between ABR neurologic measures such as inter-peak latencies and rate studies relative to neuroaudiologic findings and clinical neurological symptoms. ABR assessment will be added to the test protocol for future years.

Although preliminary, the results of this study suggest that (1) the onset of hearing loss in WS may occur earlier than what has been reported previously; (2) hearing aids may be beneficial in patients with WS; (3) some WS patients with normal hearing may have difficulty with SIN tasks; and (4) WS patients who have both low- and high-frequency SNHL may be more likely to have vestibular dysfunction. Audiologic and vestibular

function will continue to be monitored in this cohort to determine whether changes in function occur over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Pure tone AC thresholds for W01, W03, W04, and W12. Legend: O, right ear and X, left ear. Age in years at time of testing and at hearing loss diagnosis were as follows: W01, 13.1 and 9.0; W03, 17.9 and 6.0; W04, 23.8 and 12.0; and W012, 22.9 and 7.0.

Figure 2.

Responses of the vestibuloocular reflex to whole-body rotations about the earth-vertical axis. Left: Sinusoidal stimulation at peak velocity of 60 deg/sec. Top, gain; bottom, phase lead of slow-phase eye movements re head velocity (deg). Right: Velocity steps (100 deg/sec). Top, gain; bottom, time constant (sec). Key indicates individual study participant tracings. Shaded areas indicate abnormal findings.