Hyperacusis in Williams syndrome: Characteristics and associated neuroaudiologic abnormalities

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Abstract—*Background:* Hyperacusis and phonophobia are common, debilitating symptoms in Williams syndrome (WS), yet little is known about their underlying audiologic and neurologic processes. *Methods:* The mothers of 49 subjects with WS were asked to complete the Hyperacusis Screening Questionnaire. Subjects with reported hyperacusis and sufficient developmental capacity underwent comprehensive audiological and brain auditory evoked response (BAER) testing. Findings were compared with those from pair-matched typically developing control subjects. *Results:* Forty-one of the 49 children with WS (84%) had hyperacusis of moderate to severe degree, which began in infancy. Of these, 21 (mean age 15.8 ± 5.5 years) were quantitatively tested. Subjects with WS reported discomfort at sound intensities on average 20 dB lower than control subjects. Pure-tone audiometry and distortion products otoacoustic emission test revealed a high-frequency cochlear hearing loss. An absence of ipsilateral acoustic reflex responses to maximum stimulation was significantly more common in the subjects with WS than controls. On BAER testing, the WS group had a significant prolongation in wave I latency. *Conclusions:* Hyperacusis in Williams syndrome (WS) is associated with a high-frequency hearing loss resembling the configuration of noise-induced hearing loss. The hyperacusis and hearing loss in WS may stem from a deficiency in the acoustic reflex resulting from auditory nerve dysfunction. Additional mechanisms that may mediate hyperacusis in WS and should be evaluated in future studies include recruitment, malformation of the facial canal, and haploinsufficiency of the elastin gene.

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Williams syndrome (WS) is caused by a approximately 1.5-Mb chromosomal microdeletion at band 7q11.23.[1] The estimated incidence is 1 in 8,000 live births.[2] WS is a multisystem disorder manifested by a wide range of medical diseases and a unique behavioral and cognitive profile.[3-5] A salient feature of subjects with WS is a strong attraction to music.[6] Imaging and postmortem studies suggest that the musicality may be related to an increased activation of the amygdala, enlarged superior temporal gyrus, and loss of planum temporale asymmetries.[7-9]

Two additional auditory phenomena peculiar to WS are hyperacusis and phonophobia.[10,11] Hyperacusis is an oversensitivity or excessive perception of normal environmental sounds,[11] and phonophobia is an aversion to or morbid fear of normal sounds.[12] These symptoms apparently begin before 1 year of age and tend to decrease somewhat during adolescence. The behavioral reactions may be extreme and include covering the ears, crying, or avoiding noise-related situations. For example, children with WS may refrain from going to birthday parties because of fear of the noise of bursting balloons.[10,11] The associated suffering was eloquently described to us by a 16-year-old girl: "When I hear the sound of an electric drill, I feel as if it is drilling into my body."

Although the hyperacusis in WS is a debilitating problem, research into its etiology and pathophysiology has been limited. A previous study[11] found that 61% of subjects with WS had a history of otitis media, but there was no correlation between the frequency of otitis media and the presence or severity of hyperacusis. Two case series reported sensorineural hearing loss in 3 of 9 children[13] and in 12 of 16 adults with WS.[14]

In this study, we sought to further delineate the clinical characteristics of hyperacusis and phonophobia in WS and to investigate the audiologic and neurologic abnormalities in subjects with WS and hyperacusis.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the February 14 issue to find the title link for this article.

Methods. *Subjects.* The study consisted of two stages. In the first stage, using information received from the Israeli Williams Association, we asked 49 mothers of subjects with WS to complete

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a telephone interview screening for the presence of hyperacusis in their child. In the second stage, subjects reported to have hyperacusis in stage 1 who were of sufficient developmental capacity were asked to undergo comprehensive neuroaudiologic testing. Their findings were compared with those of typically developing subjects pair-matched for sex and age with no present or past history of hyperacusis who underwent the same tests.

The study protocol was approved by our institutional review board, and written informed consent was obtained from the study participants and their parents after the examination procedures were fully explained to them.

Hyperacusis Screening Questionnaire. We formulated a Hyperacusis Screening Questionnaire to study the clinical characteristics of hyperacusis in WS (see appendix E-1 on the *Neurology* Web site at www.neurology.org). The first two items read as follows: "Is your child presently frightened or bothered by certain sounds?" and "Has your child ever been bothered by sounds in the past?" If the mother replied negatively to both, the interview was terminated; if she responded positively to at least one item, the full questionnaire was completed.

Audiologic testing. All audiologic tests were performed by certified and experienced audiologists at an institute for audiology and clinical neurophysiology in a tertiary pediatric medical center.

The external and middle ear were assessed by otoscopy and by tympanometry and acoustic reflexes (AZ26 Middle Ear Analyzer, Interacoustic, Assens, Denmark). Otoscopy documents signs of otitis media or any abnormality of the tympanic membrane and canal. Tympanometry identifies possible middle ear abnormalities according to the type of tympanogram the test yields: normal, flat curve, or negative pressure.[15] The most frequent abnormality is middle ear fluid (serous otitis media).

Pure-tone audiometry was performed in a sound-attenuated room using GSI-61 audiometers (Grason-Stadler, Madison, WI) and a calibrated earphone (TDH-49) conforming to the specifications of the International Standards Organization.[16] Air and bone conduction thresholds (lowest level at which the frequency is barely heard) were measured in each ear separately at frequencies of 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz.

Tests for the most comfortable loudness level (MCL) and uncomfortable loudness level (UCL) were performed subsequent to the audiogram to quantify loudness perception. The MCL and UCL were determined for each frequency between 0.25 and 8 kHz. A continuous pure tone was presented to the subjects, beginning at the speech reception threshold (SRT) level and gradually increasing by 5-dB increments. Subjects were instructed to judge the loudness of the signal by selecting among three options: "very soft," "comfortable," and "uncomfortably loud." For each frequency, the subjects first determined the level that felt most comfortable and then the level that felt uncomfortably loud.

The SRT test was used to identify the lowest decibel level at which the patient could correctly repeat 50% of the spondaic (dual-syllable) words presented. The SRT test was followed by the word recognition test to determine speech discrimination. The test was performed separately for each ear using "phonetically balanced" monosyllabic words. The score represented the percentage of words repeated correctly at suprathreshold levels (35-dB hearing level [HL] above SRT).

The ipsilateral acoustic reflex threshold, the lowest stimulus level that produces a detectable change in acoustic admittance, was recorded for pure-tone signals at 1, 2, and 4 kHz as well as for wideband noise signals. Absence of the acoustic reflex (AR) was defined as a failure to elicit the AR at the maximum stimulation level of 110 dB.

Distortion products otoacoustic emissions (DPOAEs) reflect the activity of the cochlear outer hair cells. Specifically, low or absent DPOAE amplitudes in the presence of intact otoscopy and tympanometry findings may indicate a dysfunction of the outer cochlear hair cells. During the test, two close pure tones (f1 and f2 primaries) are presented to the ear. Because tones are close in frequency, they interact, resulting in an acoustic distortion, which in humans ranges from 2f1 to f2. Using an IL092 (F) Otoacoustic Distortion Product Analyzer (version 1.35; Oto Dynamics Ltd, Hatfield, Herts, UK), we recorded DPOAEs to primaries (f1/f2) at a ratio of 1.22, with L1 equal to L2 intensities of 70-dB sound pressure level (SPL), corresponding to the audiometric frequencies of 1, 1.5, 2, 2.5, 3, 4, 5, and 6 kHz. We used the 70-dB SPL stimulation because we were mostly interested in the configuration of the audiogram, not the hearing level, per se. The technical details of the procedure have been described elsewhere.[17]

Table *Type and characteristics of frightening or bothering sounds*

Type of sounds	n (%)	Intensity	Frequency	Continuity
Electric machines	33 (67.3)	High	High	Continuous
Thunder	27 (62.8)	High	High	Impulsive
Balloon bursting	27 (62.8)	High	Low	Impulsive
Fireworks	27 (62.8)	Very high	Low	Impulsive
Siren, alarm	25 (58.1)	High	Low	Variable
Shouting	19 (44.2)	Very high	Low	Impulsive
Loud music	18 (41.9)	High	Broad band	Continuous
Motor vehicle	13 (30.2)	High	Medium	Continuous
Hammer	8 (18.6)	High	Low	Impulsive
Barking	6 (14.0)	High	Low	Bursts
Conversation	6 (14.0)	Moderate	Low	Continuous
Crying	5 (11.6)	High	Medium	Continuous
Whistle	4 (9.3)	Moderate	Medium	Bursts
TV	3 (7.0)	Moderate	Medium	Continuous
Applause	3 (7.0)	High	High	Impulsive
Telephone	2 (4.7)	Moderate	Medium	Bursts

Brainstem auditory evoked responses (BAERs) are composed of several voltage deflections that occur within the first 15 milliseconds after stimulus onset. These deflections (peaks and troughs) represent the far-field synchronous activity produced by the onset responses of neural elements and abrupt bends in the neural fiber tracts of the eighth nerve and the auditory brainstem pathway.[18] BAERs were recorded as the potential difference between the vertex and mastoid ipsilateral to the stimulated ear. The ground electrode was placed in the contralateral mastoid. The latencies of BAER components I, III, and V were measured, and interpeak latency differences were calculated from the absolute latency data. To alleviate potential discomfort to the subjects stemming from their sensitivity to noise, the evocative stimulation level was reduced to 70-dB HL using alternating polarity clicks, at a rate of 11 clicks/s, presented to the ear by insert phone. A frequency analysis of the clicks revealed a concentration of energy between 1.5 and 3 kHz. The potential difference between the vertex and ipsilateral mastoid was amplified at a band pass of 0.1 to 3 kHz (3 dB down, 6-dB/octave slopes), and 1,024 sweeps were averaged to obtain the BAERs.

Data analysis. Data were analyzed using BMDP statistical software.[19] Values are presented as means ± SD. Whenever there were no significant differences between the right and left ear measures, we calculated the mean value of the two to simplify the reportage of the results. The frequency of the absence of an ipsilateral AR in subjects with WS and control subjects was compared using Pearson χ^2 test or Fisher exact test, as appropriate. Pure-tone audiogram measures, MCL and UCL, DPOAEs, and BAER were compared between the groups using analysis of variance (ANOVA) with repeated measures. Mean SRTs and word recognition test scores were compared using unpaired *t* test.

Results. *Screening for hyperacusis.* The study group included 20 male and 29 female subjects with WS of mean ± SD age of 11.1 ± 7.4 years (range 1 to 35 years). Of these, 41 (83.7%) were reported by their mothers to be frightened or bothered by normal environmental sounds (table); most were sensitive to more than one sound (average 3.6 ± 2.9 sounds). The hyperacusis was most severe at age 5.7 ± 3.8 years and tended to decline thereafter. The most common behavioral responses were covering the ears (67.4%), leav-

ing the area (62.8%), complaining (51.4%), crying (44.2%), hugging (25.6%), asking to stop the noise (16.3%), panic behavior (14.0%), and getting into bed (14.0%). Most events of hyperacusis were associated with high intensity noises of low-medium frequency and variable degrees of continuity (table). On a scale of 1 to 5, the mean rating of the degree to which noise sensitivity interfered with the children's lives was 3.5 ± 1.0, considered moderate (grade 3: "markedly distracts the child or make the child stop his/her activity") to severe (grade 4: "runs away from the site of the sound or needs to be prepared before going to a place where he or she will be exposed to the sound").

Audiologic and BAER tests. Twenty-one of the 41 children with reported hyperacusis underwent comprehensive audiologic testing. This subgroup included 16 female and 5 male subjects of mean age 15.8 ± 5.5 years (range 6 to 26 years). The other 20 subjects were excluded because their low cognitive level (n = 5) or young age (<6 years; n = 12) made cooperation during the procedure impossible or because the child chose not to participate in the audiologic evaluation (n = 3). All 21 subjects tested had a moderate to severe degree of hyperacusis according to the screening.

Otoscopy revealed no abnormalities in 20 of the 21 children (95.2%). One subject had mild right-side serous otitis media and bilateral tympanic membrane atelectasis. An abnormal tympanogram (middle ear negative pressure) was noted in four subjects (19%; two bilateral and two unilateral), indicating mild serous otitis media. All control subjects had normal otoscopy and tympanometry findings.

The pure-tone audiograms of the left and right ears of the children with WS and the control subjects are shown in figure 1. ANOVA with repeated measures revealed between-group differences for the right ($p < 0.001$) and left ears ($p < 0.001$), and an interaction of audiogram frequency thresholds × group for both ears ($p < 0.001$). Hearing thresholds were higher bilaterally in the WS group than in the control group for medium to high frequencies (3 to 8 kHz).

Two children with WS (10%) had a conductive hearing loss in the frequency range of 0.25 to 2 kHz, and 12 (60%) had a high-frequency cochlear hearing loss, defined as bone conduction thresholds above 25 dB in the frequency range of 3 to 8 kHz. The severity of the high-frequency hearing loss ranged from 25 to 55 dB on the right and 25 to 110 dB on the left. In 9 of the 12 patients, the high-frequency hearing loss was bilateral.

UCL testing at pure-tone frequencies of 0.25 to 8 kHz yielded a between-group difference on ANOVA with repeated measures ($p < 0.001$), with an interaction of pure-tone frequencies × group ($p < 0.05$). As shown in figure 2, across all frequencies, subjects with WS reported discomfort at lower intensities than control subjects. No such findings were noted for MCL at the same range of frequencies. There was no significant correlation between severity of hearing loss by audiometry and UCL.

Mean SRTs were higher in the patients with WS than in the control subjects (11.1 ± 6.4 vs 5.8 ± 1.8 dB; $p < 0.001$), although the values were within normal limits. No between-group difference was noted on the word recognition test (99.1 ± 2.1% and 99.7 ± 1.1%), indicating that speech comprehension was intact in quiet conditions.

An absence of ipsilateral AR responses to maximum stimulation and across all frequencies was noted more often in the WS group than in the control subjects (figure 3). The differences were significant, after correcting for multiple comparisons, at 1 kHz (71.4 vs 28.6%), 2 kHz (61.9 vs 16.7%), and wide-band signals (67.7 vs 28.6%) ($p < 0.01$ for all) and nonsignificantly higher at 4 kHz (71.4 vs 45.2%).

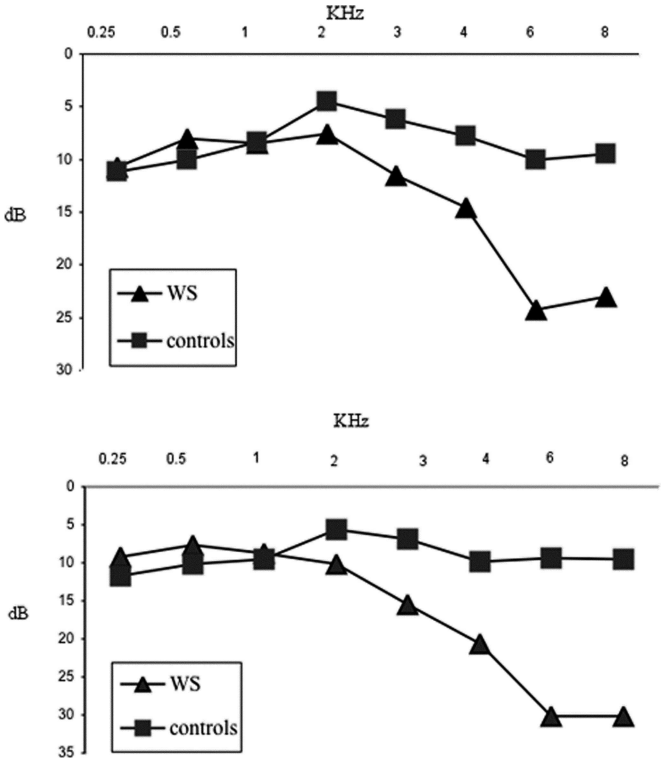

Figure 1. Pure-tone audiometry in subjects with Williams syndrome (WS) compared with typically developing control subjects. The top panel shows data for the right ear; bottom panel, left ear.

Repeated-measures ANOVA of DPAOEs yielded a between-group difference ($p < 0.005$) and within-group difference ($p < 0.01$). As shown in figure 4, DPOAE amplitudes were lower in the WS group than in control subjects, indicating a dysfunction of the outer hair cells and suggesting a cochlear dysfunction, especially in the medium to high frequencies. DPOAEs could not be produced in five subjects with WS (23.8%).

Repeated-measures ANOVA of BAERs yielded a

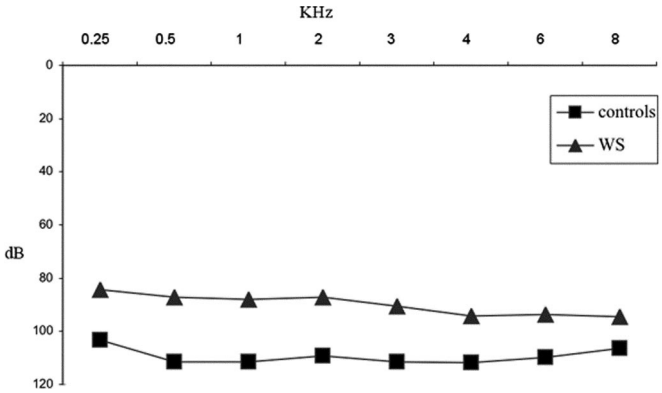

Figure 2. Uncomfortable loudness levels in subjects with Williams syndrome (WS) vs typically developing control subjects.

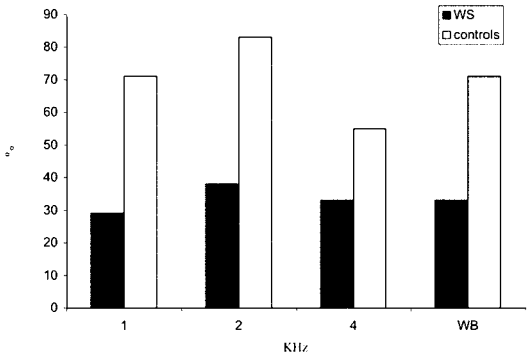

Figure 3. Comparison of proportion of subjects (%) with Williams syndrome (WS) vs typically developing control subjects with no ipsilateral acoustic reflex at maximum stimulation level in 1, 2, and 4 kHz and in wide band (WB).

between-group difference ($p < 0.05$). Compared with control subjects, subjects with WS had a prolonged absolute latency of waves I (1.78 ± 0.22 vs 1.63 ± 0.17), III (3.98 ± 0.48 vs 3.70 ± 0.16), and V (5.90 ± 0.74 vs 5.52 ± 0.17). On the basis of our general population norms with 2 SD considered the normal range, 13 subjects with WS had abnormal latencies for wave I (61.9%), 9 for wave III (42.9%), and 5 for wave V (23.8%). Interpeak latencies (I to III, III to V, I to V) were similar in the two groups, ruling out an impairment in neuronal conduction in the brainstem tracts in WS and implying that the prolongation in the latency of waves III and V was attributable to the prolongation in wave I latency (figure 5).

Discussion. In this study, hyperacusis occurred in 84% of the subjects. The most frequent sounds of daily life to which the children were sensitive included electric machines, thunder, bursting balloons, and fireworks. The children responded with marked fear and exhibited aversive behaviors. According to the maternal interviews, aversive responses to noise (crying and exaggerated startle response) were present already in infancy. The hyperacusis peaked

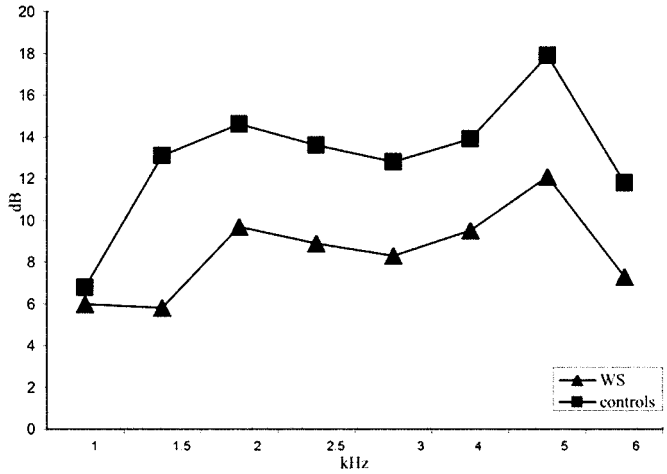

Figure 4. Distortion product otoacoustic emissions (DPAOEs) in subjects with Williams syndrome (WS) vs typically developing control subjects.

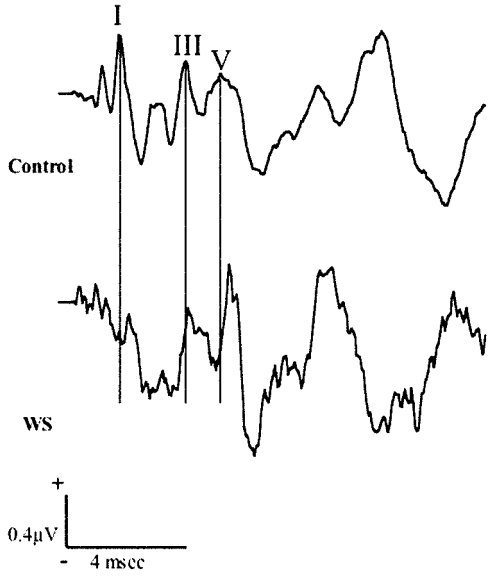

Figure 5. Brainstem auditory evoked response (BAER) traces showing a prolongation of waves I, III, and V in a subject with Williams syndrome (WS) compared with a typically developing control subject.

at age 5.7 years compared to 7 with 10 years in typically developing children[20] and tended to decrease somewhat thereafter. Quantitative evaluation of the hyperacusis showed that the discomfort level in the study group was on average 20 dB lower than in the control group (figure 2).

In most cases of hyperacusis, hearing is normal.[13] However, subjects with WS in our study exhibited cochlear high-frequency hearing loss on pure-tone audiograms. The hearing loss was associated with lower DPOAE amplitudes across a wide frequency range, but primarily in the high frequencies, reflecting a dysfunction of the outer hair cells, especially in the basal turn of the cochlea. Cochlear hearing loss is frequently accompanied by recruitment, that is, a rapid increase in perceived loudness in threshold level stimulation.[13] Future studies should evaluate whether recruitment is a common phenomenon in subjects with WS.

Only 10% of our subjects with WS had conductive hearing loss. Although an earlier study suggested that the hearing loss in WS is conductive,[11] our finding agrees with case series reports of high-frequency cochlear hearing loss in children and adults with WS.[13,14]

The asymmetric configuration (left > right) of the cochlear hearing loss in WS closely resembles the typical hearing loss induced by repeated exposure to high-level noise in typically developing subjects.[21,22] Nevertheless, none of the children in our sample were exposed to noise at a high-risk level (>85 dB for 8 hours daily), and all were living in a normal environment, like the typically developing control subjects, in whom no cochlear hearing loss was found. The noise-induced hearing loss pattern is extremely rare in typically developing children.

Another major finding of our study is the absence

of an ipsilateral AR, which could not be evoked in a high proportion of children with WS at maximal stimulus levels. The primary role of the AR is assumed to be control of the input to the inner ear and protection of the auditory system against loud sounds. Thus, it seems plausible that the hyperacusis in subjects with WS is partially attributable to their deficiency in this defensive reflex. This assumption is supported by studies showing that absence of the AR results in high-frequency hearing loss.[23]

The efferent part of the AR depends on facial nerve innervation of the stapedial muscle, which fixates the stapes and attenuates the sounds transmitted to the cochlea.[15] Although abnormal AR thresholds and hyperacusis have also been reported in patients with Bell palsy,[24] to our knowledge, WS is not associated with symptoms of facial nerve paralysis, such as gross facial asymmetry, excessive tearing, and taste disturbances. However, subjects with WS have neurocranial abnormalities, including thickening of the cranial bones.[25] Thus, it is possible that subjects with WS have a malformation of the facial canal, which may lead to trapping of the facial nerve. Further assessments using electromyography, taste tests, and petrous bone imaging are needed to corroborate this assumption.

The afferent arm of the AR depends on an intact transmission of the stimulus from the cochlea to the auditory nerve. Thus, an AR deficiency may be linked to cochlear impairment. However, a total absence of reflex responses is rare for hearing losses of less than about 80 dB HL.[26] In our sample, the hearing loss was mostly in 4- to 8-kHz range and of mild to moderate severity only. Furthermore, the AR was not evoked even in WS subjects with a normal audiogram. Therefore, it is unlikely that the absence of AR was attributable to the cochlear hearing loss.

A more plausible explanation of the absence of an AR is a dysfunction of the auditory nerve, as indicated by the prolongation of BAER wave I. The source of the delayed responsiveness of the acoustic nerve in our sample requires further study. It may be the result of an abnormal underlying mechanism, such as desynchronization of the auditory nerve fibers or a dysfunctional interaction between the nerve endings and the inner hair cells.

Absence of the AR and an abnormal BAER are also common in auditory neuropathy.[27] However, in auditory neuropathy, hyperacusis is rare, and the DPOAEs are preserved, as there is no cochlear pathology. In addition, the hearing loss tends to be more severe than in WS and is not, like in WS, limited to the high frequencies. The BAER is also extremely distorted, and speech discrimination, which is intact in WS, is poor.[27]

The onset of the hyperacusis and exaggerated startle response already in infancy suggests that the lack of an AR is related to anomalies in one of the genes from the WS region of deletion. Of the 24 genes that have been identified in the critical region, only the elastin gene (*ELN*) has been definitely associated with a phenotype of WS, namely, supravalvular aortic stenosis.[28] Elastin is not expressed in neurons, but it is expressed in blood vessels of the brain. A haploinsufficiency of the elastin gene in WS could mediate the hyperacusis by a peripheral mechanism. Specifically, the shearing motion of the stereocilia in response to vibrations, which opens the ion channels and leads to depolarization of the hair cells, depends on their actin cytoskeleton and elastic extracellular filaments. Although the exact contents of the extracellular link remain unclear, studies have reported that elastase enzyme disintegrate tip links.[29] An elastin deficiency in WS can lead to a desynchronized movement of the stereocilia, resulting in hearing loss and delayed cochlear nerve activation.

Studies of subjects with smaller deletions in the 7q11.23 region and of knockout mice may direct us to the gene that is related to hyperacusis. So far, however, these types of studies have not included hyperacusis as one of the phenotypes investigated.[30-32] Another candidate gene in hyperacusis in WS is the *LIMK-1* gene from the 7q11.23-deleted region. *LIMK-1* is widely expressed in the mammalian CNS, and its interaction with the cytoskeleton protein actin is essential for neuron migration and function.[28] Interestingly, a study of *LIMK-1* knockout mice found that in a fear-conditioning test, the study mice showed significantly longer and more constant freezing in response to a sound than wild-type mice.[33]

WS has been a focus of research mainly because of its unique cognitive and social profile. However, the hyperacusis and phonophobia associated with the syndrome, though very common and debilitating, have been relatively neglected, and their pathophysiologic mechanisms are poorly understood. Taken together, our findings suggest that the cochlear impairment in WS is due to repeated noise stimulation in the absence of the appropriate protection normally provided by the acoustic reflex. The hyperacusis could be the result of the combination of cochlear hearing loss and auditory nerve dysfunction, which probably alters the perception of loudness in the afferent auditory system.

This study has clinical implications, as it seems that sounds of 70 to 80 dB, which do not cause harm in normal subjects, may damage the cochlea in subjects with WS, and induce a hearing loss that clinically resembles noise-induced hearing loss. This indicates that the standard treatment of hyperacusis and phonophobia, which is based on behavioral desensitization to noises by repeated exposure,[34] may be inappropriate in WS.

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