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Audiological follow-up of 24 patients affected by Williams syndrome

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ABSTRACT

Williams syndrome is a neurodevelopmental disorder associated with cardiovascular problems, facial abnormalities and several behavioural and neurological disabilities. It is also characterized by some typical audiological features including abnormal sensitivity to sounds, cochlear impairment related to the outer hair cells of the basal turn of the cochlea, and sensorineural or mixed hearing loss, predominantly in the high frequency range. The aim of this report is to describe a follow-up study of auditory function in a cohort of children affected by this syndrome. 24 patients, aged 5–14 years, were tested by means of air/bone conduction pure-tone audiometry, immittance test and transient evoked otoacoustic emissions. They were evaluated again 5 years after the first assessment, and 10 of them underwent a second follow-up examination after a further 5 years. The audiometric results showed hearing loss, defined by a pure tone average >15 dB HL, in 12.5% of the participants. The incidence of hearing loss did not change over the 5-year period and increased to 30% in the patients who underwent the 10-year follow-up. Progressive sensorineural hearing loss was detected in 20% of the patients. A remarkable finding of our study regarded sensorineural hearing impairment in the high frequency range, which increased significantly from 25% to 50% of the participants over the 5-year period. The increase became even more significant in the group of patients who underwent the 10-year follow-up, by which time the majority of them (80%) had developed sensorineural hearing loss. Otoacoustic emissions were found to be absent in a high percentage of patients, thus confirming the cochlear fragility of individuals with Williams syndrome. Our study verified that most of the young Williams syndrome patients had normal hearing sensitivity within the low-middle frequency range, but showed a weakness regarding the high frequencies, the threshold of which worsened significantly over time in most patients.
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1. Introduction

Williams syndrome (WS), also known as Williams–Beuren syndrome (OMIM 194050), is a neurodevelopmental disorder that occurs in 1 in 7500 people [1]. It is caused by a hemizygous microdeletion of approximately 28 genes on chromosome 7 (7q11.23) [2], including the elastin gene (ELN), an important component of elastic fibres, and the gene encoding LIM kinase 1 (LIMK1), which is highly expressed in cochlear regions during embryonic development [3].

In addition to cognitive and behavioural disabilities, cardiovascular problems, facial abnormalities and short stature, individuals with WS have some typical audiological features.

An abnormal sensitivity to sounds with auditory allodynia (substantial aversion to or fear of certain sounds) and odynoacusis (lower uncomfortable loudness level) affects most children with WS [4–6]. A particular cochlear fragility connected with a dysfunction of the outer hair cells (OHC) particularly in the basal turn of the cochlea has recently been reported. This is highlighted by the absence or alteration of otoacoustic emissions in a high percentage of patients [7–11]. The cochlear impairment may be

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associated with sensorineural hearing loss, typically mild or moderate, mainly affecting the high frequencies, and described by different authors as ranging from 13.2% to 90% of patients [7,9,10,12–14]. Zarchi et al. [13] demonstrated a positive correlation between the severity of high-frequency hearing loss and age in WS patients that suggests progressive hearing loss. Serious otitis media and conductive hearing loss have been noted particularly in younger individuals affected by WS, but to a lower extent than sensorineural hearing loss [4,7,9,10,13,15,16].

Although a progressive high-frequency hearing impairment has been suggested, to our knowledge no longitudinal study has verified whether auditory sensitivity changes over time in this syndrome. The aim of this study was to perform a follow-up assessment of auditory function in a group of twenty-four children with WS, using subjective and objective procedures. All of the patients were evaluated five years after the first assessment and ten of them underwent a second follow-up examination after a further five years.

2. Patient data

A total of 24 subjects affected by WS (14 males and 10 females), with an age ranging from 5 to 14 years, participated in this study. The mean age was 8.65 years (standard deviation [SD] = 2.45) at the time of the first visit (**T0**). All had the typical deletion (7q11.23) confirmed by cytogenetic fluorescence in situ hybridization analysis. They were recruited by two clinical research sites, the Neurorehabilitation Unit of IRCCS Eugenio Medea, Bosisio Parini (Lecco) and the Pediatric Department of the University of Milan, Italy, where they were followed by a multidisciplinary medical team. All of the parents of the children who were asked to take part in this follow-up study agreed to participation; there were no refusals. All of them attended the first follow-up visit, but 14 did not come to the third control and therefore did not complete the follow-up. The audiological tests were performed at the Audiological Unit of IRCCS Eugenio Medea, Bosisio Parini (Lecco) and the Audiological Unit of the University of Milan, and were carried out by certified and trained audiometric technicians, always using the same measurement instruments.

Five years after the first visit (**T5**), all of the patients (mean age 13.67 years; SD: 2.18) underwent a second series of audiological assessments including pure-tone audiometry, immittance test and transient otoacoustic emissions.

10 participants, 5 males and 5 females (mean age 17.40 years; SD: 2.46) underwent a third set of audiological tests 10 years after the first examination (**T10**).

All of the WS participants, or their parents if they were minors or legally dependent, signed an informed consent for the use of clinical data for research purposes.

The general cognitive competencies of the WS participants were assessed by administering age-appropriate Wechsler Intelligence Scales: Wechsler Preschool and Primary Scale of Intelligence [17], Wechsler Intelligence Scale for Children Revised [18], Wechsler Adult Intelligence Scale Revised [19] and Griffiths Mental Developmental Scale – Revised [20] for younger children. The results are expressed as Full Scale IQ scores.

3. Methods

At T0, all of the patients underwent a complete audiological evaluation in a clinical setting; tests included air/bone conduction audiometry, immittance test and transient evoked otoacoustic emissions. The external ear canal and the tympanic membrane were examined by means of a routine otoscopic examination in order to detect possible external and/or middle ear disorders.

By means of *pure-tone audiometry*, we were able to measure the audiometric threshold of all patients. The tests were performed in a sound-attenuated booth using an Amplaid 309 audiometer (Amplifon, Italy) and calibrated earphones (TDH 49) according to the International Standards Organization and following the methodology described in the "Guidelines for manual pure-tone threshold audiometry" of the American Speech-Language-Hearing Association [21]. Hearing levels were measured in each ear separately at 0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz, for air conduction and at 0.25, 0.5, 1, 2, 3, 4 kHz for bone conduction.

In order to differentiate normal hearing from hearing loss, we used the pure-tone average (PTA) which refers to 0.5–1–2 kHz. To identify a hearing impairment limited to high tones, we studied the high frequency range. The high-frequency pure-tone average (HPTA) was calculated by averaging thresholds per ear obtained at frequencies of 4, 6 and 8 kHz [9]. Therefore, in this report *normal hearing* refers to a PTA equal to or lower than 15 dB HL [22,23] and *hearing loss* to a PTA above 15 dB HL. The degree of hearing loss is classified as "slight" when the PTA was between 16 and 25 dB HL, "mild" between 26 and 30 dB HL, "moderate" between 31 and 50 dB HL, "severe" between 51 and 70 dB HL and "profound" more than 71 dB HL [23]. The type of hearing loss was classified according to the audiometric results by comparing air and bone conduction thresholds [24]: *conductive hearing loss*, defined by normal bone conduction thresholds (<15 dB HL) and an air-bone gap >15 dB HL, averaged over 0.5, 1 and 2 kHz; *sensorineural hearing loss*, defined by an equal amount of loss for air and bone conduction thresholds (air-bone gap <15 dB HL, averaged over 0.5, 1 and 2 kHz); *mixed hearing loss* defined by a bone conduction threshold and an air-bone gap >15 dB HL, averaged over 0.5, 1 and 2 kHz. Hearing loss was considered *progressive* if the PTA deteriorated by more than 15 dB HL within a 10 year period [24].

Tympanometry and measurement of acoustic reflex (*AR*) were carried out using the Interacoustics AZ26 equipment in order to study middle ear function. Tympanograms were recorded using a 226-Hz probe tone. For each tympanogram, the *peak pressure* (PP) and *static compliance* (SC) were calculated and expressed in daPa and mL respectively. The tympanograms were classified as follows: *Type A* (normal middle ear pressure) defined by a sharp peak, a PP between −99 and +50 daPa and a SC within the range of 0.3–1.6 mL; *Type B* (flat curve): no peak, no measurable SC; *Type C* (negative peak pressure): sharp peak, PP <−99 daPa, SC = 0.3–1.6 mL; *Type As* ("shallow" peak: low static compliance): shallow peak, PP between −99 and +50 daPa, SC <0.3 mL; *Type Ad* ("deep" peak: high static compliance): sharp peak, PP between −99 and +50 daPa, SC >1.6 mL [25–27].

In patients with type A tympanograms, we determined the contralateral AR using pure-tone signals at 0.5, 1, 2 and 4 kHz at 80 dB HL. The intensity of the eliciting stimuli was increased in 5 dB steps until the onset of the reflex; the AR was considered absent if not recorded at the maximum stimulation level. We chose to evaluate the contralateral AR because the ipsilateral AR measurement can be affected by artifacts.

Transient Evoked OtoAcoustic Emissions (*TEOAEs*) were measured in order to assess the activity of the OHC of the cochlea. The test was carried out in a sound attenuated booth, using an Otodynamics ILO-292 DP system with ILO-V5 software. TEOAEs were recorded in patients showing normal middle ear function upon otoscopic examination, type A tympanogram and the presence of ARs. The stimuli consisted of trains of clicks at 70 dB peak SPL presented at a rate of 50/s, according to the 'non-linear' recording protocol. Each click lasted 80 μs. The analysis time was 20 ms, and the ear-canal signal was bandpass-filtered from 0.5 to 6 kHz. For each recording, 260 responses were averaged with the default rejection threshold. The TEOAE responses obtained were interpreted using

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