Cochlear Dysfunction Is a Frequent Feature of Facioscapulohumeral Muscular Dystrophy Type 1 (FSHD1)

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**INTRODUCTION**

Facioscapulohumeral muscular dystrophy (FSHD) is the most common form of hereditary muscle disease after Duchenne’s dystrophy and Steinert’s myotonic dystrophy.

**Results:** All FSHD1 patients showed significantly reduced DPOAEs and TEOAEs, bilaterally and at all frequencies, even when considering only subjects with a normal PTA or a mild muscular involvement (FSHD score ≤ 2). No correlation between OAEs and FSHD clinical score was found.

**Discussion:** Cochlear echoes represent a sensitive tool in detecting subclinical cochlear dysfunction in FSHD1 even in subjects with normal hearing and/or subtle muscle involvement. Our study is focused on the importance of evaluating the cochlear alteration through OAEs and, in particular, by performing TEOAEs and DPOAEs sequentially, to evaluate more frequent specificities of cochlear dysfunction with a wider spectrum of analysis. **Key Words:** Cochlear damage—DPOAE—FSHD—Otoacoustic emissions—TEOAE.

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has a more complex pattern of inheritance since it is more likely a digenic disease (4). Indeed, as for FSHD1, the clinical expression of FSHD2 depends on a specific chromosome-4 haplotype that contains a polyadenylation (pA) signal distal to the last repeats, in addition to the open chromatin structure (5).

FSHD1 is characterized by a great clinical variability with the typical muscular symptoms and, in some cases, additional clinical features such as vascular retinopathy, mental retardation, epilepsy, and hearing loss (1,6,7). Patients with childhood onset of the disease may have a significant hearing loss, while the typical cases might be present with a milder bilateral sensorineural hypoacusis predominantly on high frequencies (8). Previous studies have shown a hearing impairment in FSHD1 through pure tonal audiometry (PTA) and auditory brainstem response (ABR) (9). These studies, however, were mainly case reports and in some instances, reported controversial findings (10,11).

Otoacoustic emissions (OAEs) represent an objective, noninvasive and a simple auditory investigation, which provide suitable information on cochlear status. OAEs are generated by the contractile activity of a particular type of cochlear cells, named “outer hair cells” (OHCs), which are responsible for cochlear sound amplification and can be detected spontaneously or in response to particular auditory stimuli, including those generated by OAEs. This active movement of OHCs is transmitted from the cochlea to the middle ear, where it generates a modification of pressure on tympanic drum, which is easily recordable by a microphone fitted into the external ear canal. Among the main types of OAEs, transient evoked otoacoustic emissions (TEOAEs) are perhaps the best known because of their wide clinical application in newborn hearing screening programs. They represent a sensitive tool for detecting cochlear dysfunction in patients with hypoacusis that do not exceed 30 to 40 dB HL. Otherwise, distortion product otoacoustic emissions (DPOAEs) provide information also in patients with mild-to-moderate hearing loss and with a wider frequency spectrum of observation (above 10 kHz). Therefore, DPOAEs represent an accurate instrument for the evaluation of auditory function, independent from the results of pure-tone audiometry (PTA) evaluation, which in some cases may be “normal,” despite the presence of an underlying cochlear dysfunction (12).

Previous studies have assessed auditory function in several neuromuscular diseases including FSHD1; however, cochlear function has rarely been explored in muscular dystrophies (13) and a single study has reported this issue in FSHD by performing TEOAEs analysis (14). To explore this clinical aspect, we studied OHCs function in a cohort of FSHD1 patients by performing TEOAEs and, to amplify the spectrum of observation, DPOAEs. In addition, we performed contralateral acoustic stimulation (CAS) to evaluate the integrity of the medial olivocochlear system (MOC), also known as the “efferent acoustic pathway.”

**METHODS**

The study involved 26 consecutive FSHD1 patients referring to the Neuromuscular Diseases Unit of Tor Vergata University Hospital in Rome between January 2018 and February 2019 and a control group of 38 consecutive “healthy” subjects referring to the Otorhinolaryngology Department of Tor Vergata University Hospital for a routine audiological evaluation between January and December 2018. The subjects were enrolled in the bases of age between 18 and 80 years and a positive genetic test confirming the presence of one D4Z4 allele of reduced size. Exclusion criteria, both for patients and controls, were represented by a documented personal history of hearing dysfunction, the evidence of otological, and/or labyrinthine disorders highlighted by the clinical evaluation, an anamnesis of previous and noise exposure (e.g. professional and/or recreational) and/or any previous reported ototoxic drug consumption. The study was approved by the Ethics Committee of Tor Vergata University Hospital and all the enrolled subjects signed an informed consent to participate in this study.

**Neurological Evaluation**

All patients underwent general neurological examination and the Comprehensive Clinical Evaluation Form (CCEF) (15). Neurological examination included the assessment of 14 muscle and muscle group function on either side (pectoralis, extratorotators of upper limb; triceps brachialis, biceps brachialis, wrist flexors, wrist extensors, long finger flexors, common finger extensor, gluteus maximus, iliopectoas, biceps femoris, quadriceps, triceps surae, tibialis anterior) according to the Medical Research Council (MRC) scale for muscle strength. The CCEF includes the Evaluation Form (CCEF Section 1), the FSHD Evaluation Scale (CCEF Section 2), the Clinical Diagnostic Form (CCEF Section 3) and the Clinical Categories (CCEF Section 4), and investigates typical and atypical clinical features of FSHD. The CCEF identifies four different categories: 1) subjects presenting various degrees of facial and scapular girdle muscle weakness, typical of FSHD (category A, subcategories A1–A3); 2) subjects with muscle weakness limited to scapular girdle or facial muscles (category B subcategories B1, B2); 3) asymptomatic/healthy subjects (category C, subcategories C1, C2); 4) subjects with myopathic phenotype presenting atypical clinical features not consistent with FSHD canonical phenotype (D, subcategories D1, D2). We worked on the validated and standardized FSHD evaluation scale (CCEF section 2) to score the disease severity to compare it with the hearing findings (16). This FSHD clinical score ranges from 0 to 15 points, where 0 means asymptomatic and 15 seriously affected. Clinical measurements were performed by the same neurologist, to minimize variability.

**Audiological Evaluation**

All subjects underwent a complete otological evaluation at the Department of Otolaryngology at Tor Vergata University Hospital. This included an otological history, otoscopic examination, PTA, considering each ear separately and for each pure-tone frequency stimulation (from 125 to 8000 Hz) and an acoustic impedance test to evaluate the integrity of the tympanic membrane and the intensity threshold of the acoustic reflex for each ear, using 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz stimulus tones. The stimulus was given either to the same ear as a compliance probe (ipsilateral reflex) or to the opposite ear (contralateral reflex). According to the “International American Speech-Language-
Hearing Association (ASHA)” criteria, we defined hearing impairment severity as follows: mild: 21 to 40 dB; moderate: 41 to 55 dB; moderately severe: 56 to 70 dB; severe: 71 to 90 dB; and profound: > 90 dB; for at least one tested frequency for either ear (17). In the same session, TEOAEs and DPOAEs were recorded sequentially for both ears using Otodynamics ILO analyzer software (MAICO MI 34; Berlin, Germany). All audiological tests were performed in the audiology booth of the Department of Otorhinolaryngology of Tor Vergata University Hospital, which is located away from noisy and crowded spaces. Moreover, to avoid any possible disturbance, we asked participants to turn off all their electronic devices and recommended to the accompanying person to remain silent in the waiting room. The ambient noise level was recorded before testing by our audiometric technician (G.N.) through the use of an environmental microphone and all the exams were performed according to the International Criteria for the “Maximum Permissible Ambient Noise Level” for audiometric test rooms (18).

The OAEs probe was placed and calibrated by using an automated measurement system before each test and then positioned in the external ear canal. We focused our study on the frequencies of 1, 1.5, 2, 3, 4, 6, and 8 kHz. DPOAEs are produced in response to two different sound stimuli presented simultaneously (identified with two frequencies named “f1” and “f2”), which generate nonlinear cochlear responses, consisting in the production of a new frequency at the cochlear level.

Finally, to explore the integrity of the MOC efferent system, we recorded TEOAEs and DPOAEs of both ears using a contralateral broadband noise (CAS) at 65 dB sound pressure level for all the tested frequencies, considering the suitable stimulation frequency for MOC evaluation as previously suggested (19).

### Statistical Analysis
Categorical values are reported as frequencies (%), and continuous variables showed a normal distribution confirmed by the histograms and Kolmogorov–Smirnov test. A comparison of continuous variables among groups was performed by T test for each frequency. A p value of < 0.05 was considered statistically significant. Pearson’s correlation test was performed. All data have been analyzed by using the SPSS, version 21 (IBM, Armonk, NY) and Prism 7 (Graphpad Software, Inc., San Diego, CA).

### RESULTS

#### Demographic and Clinical Data
Demographic and clinical data are reported in Table 1. We enrolled 26 consecutive patients, 10 female and 16 male (mean age 53 yr, range 18–77) with 33 years as mean age at onset (range 14–60) and a mean of 20 years of disease duration. Mean length of EcoRi fragment was 23 kb (range 17–32 kb). FSHD clinical score ranged from 0 to 13 with a mean of 5.7 points. By the CCEF, we found 54% of patients with the classical phenotype class A (2, 3, and 9 patients with class A1, A2, and A3 respectively), 27% with class B (6 and 1 patients with class B1 and B2 respectively), 27% with class C (6 and 1 patients with class B1 and B2 respectively), and 27% with class D (6 and 1 patients with class B1 and B2 respectively).

#### Table 1. Demographic and clinical data of patients

| No | Sex | Age | Onset | Disease Duration | EcoRi Fragment (kb) | FSHD Score | Class | Family | Hearing Complaints | PTA |
|----|-----|-----|-------|------------------|---------------------|------------|-------|--------|-------------------|-----|
| 1  | F   | 62  | 33    | 29               | 22                  | 8          | D     | 1      | –                 | Normal |
| 2  | F   | 54  | 16    | 38               | 20                  | 7          | D     | 2      | –                 | Mild  |
| 3  | F   | 46  | 35    | 11               | 20                  | 2          | B1    | 2      | –                 | Normal |
| 4  | M   | 52  | 17    | 32               | 19                  | 10         | A1    | 3      | –                 | Mild  |
| 5  | M   | 65  | NA    | NA               | 17                  | 6          | A3    | 4      | +                 | Moderate |
| 6  | M   | 28  | 15    | 13               | 19                  | 1          | B1    | 5      | –                 | Normal |
| 7  | M   | 60  | 20    | 40               | 19                  | 3          | A3    | 5      | –                 | Mild  |
| 8  | F   | 56  | 49    | 7                | 21                  | 10         | A3    | 6      | –                 | Normal |
| 9  | M   | 48  | 40    | 8                | 21                  | 4          | A2    | 6      | –                 | Normal |
| 10 | F   | 50  | 28    | 22               | 32                  | 13         | A3    | 7      | –                 | Mild  |
| 11 | F   | 54  | 40    | 14               | 29                  | 7          | A2    | 8      | –                 | Normal |
| 12 | M   | 49  | A     | 0                | 22                  | 0          | C2    | 9      | –                 | Normal |
| 13 | M   | 76  | 20    | 56               | 22                  | 10         | D     | 9      | +                 | Mild  |
| 14 | M   | 54  | 28    | 26               | 20                  | 8          | A3    | 10     | –                 | Normal |
| 15 | M   | 45  | 40    | 5                | 28                  | 1          | B1    | 11     | +                 | Mild  |
| 16 | M   | 39  | NA    | NA               | 28                  | 1          | B1    | 11     | –                 | Normal |
| 17 | M   | 70  | 60    | 10               | 28                  | 7          | A2    | 11     | –                 | Mild  |
| 18 | M   | 55  | 49    | 6                | 21                  | 11         | A3    | 12     | –                 | Mild  |
| 19 | M   | 52  | 40    | 12               | 26                  | 2          | B1    | 13     | –                 | Normal |
| 20 | M   | 66  | 14    | 52               | 23                  | 2          | B1    | 14     | –                 | Mild  |
| 22 | F   | 51  | A     | 0                | 20                  | 0          | C2    | 15     | –                 | Normal |
| 23 | F   | 77  | 60    | 17               | 20                  | 11         | A3    | 15     | +                 | Mild  |
| 24 | M   | 65  | 40    | 25               | 25                  | 9          | A1    | 16     | +                 | Mild  |
| 25 | M   | 56  | 46    | 10               | 25                  | 6          | A3    | 17     | +                 | Severe |
| 26 | M   | 18  | NA    | NA               | 27                  | 1          | B2    | 18     | –                 | Normal |

A indicates asymptomatic; NA, not applicable. +, present; −, absent.

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11% with Class D, and 8% with class C and no sign of muscular impairment. It is worth mentioning that patients within a given family usually had different phenotypes. Of 18 families screened, 7 were represented by more than 1 subject. Six of seven families showed different phenotypic categories (A, B, C, and D) but in all seven, family members belonged to different subcategories (A 1–2–3; B1–2; C1–2; D), confirming the wide phenotypic variability of FSHD. Only 23% of patients reported hearing complaints.

**Audiological Tests**

Objective examination and acoustic impedance test revealed that all subjects had a normal tympanogram type “A” without evidence of tympanic membrane damage. PTA results showed that 50% of FSHD1 patients had a normal audiometric threshold, whereas 42%, 4%, and 4% had mild, moderate, and severe dysfunction, respectively. However, these figures were comparable to those of the HC group (Fig. 1). At the same time, no difference was detected between left and right ears.

Three patients did not undergo further audiological testing due to a severe sensorineural hearing loss (n = 2) or poor compliance (n = 1); therefore, OAEs were studied in 23 patients.

As to the results of OAEs, we observed a marked reduction of TEOAEs and DPOAEs, for each tested frequency, in FSHD1 patients as compared with HC (p < 0.0001; Fig. 2, A and B). To exclude any interference due to presbycusis, we compared a subgroup of FSHD1 patients and HC under 50 years of age, obtaining similar results (TEOAEs: p < 0.001; DPOAEs: p < 0.01).

We also analyzed a subgroup of FSHD1 patients with minor or no muscle signs (FSHD clinical score ≤ 2) and again, observed a substantial reduction in TEOAEs for each frequency (p < 0.001) and DPOAEs (p ranging between < 0.01 and < 0.0001, depending on frequency), as compared with HC. Furthermore, considering only subjects with normal PTA, either patients or HC, we found in the former one a significant reduction of TEOAEs (p ranging between < 0.05 and < 0.0001, depending on frequency) and DPOAEs (p < 0.001), for each frequency (Fig. 3, A and B). Moreover, the analysis of suppression test data for DPOAEs and TPOAEs showed no significant difference between patients and HC, considering all tested frequencies for both sides, and suggesting a preserved MOC functionality. Finally, no correlation was found between FSHD clinical score and OHCs.

**DISCUSSION**

Hearing loss in FSHD1 represents a controversial issue: the awareness about possible auditory dysfunction...
in these patients has been raised mainly by case reports (8–10). PTA examination in children with early-onset disease and large D4Z4 deletions has frequently shown hearing loss (9). On the other hand, subjects with adult-onset and mild symptoms less frequently develop a moderate bilateral, sensorineural hearing loss, predominantly on high frequencies (6,8). However, a multicenter study in a relatively large cohort of adult patients described no difference in hearing performance, as highlighted by PTA, compared with HC (20). Further studies have also evaluated auditory function through unconventional audiological methods such as ABR and TEOAEs, suggesting that hearing impairment may be a consequence of cochlear dysfunction (1,7,10,11). Moreover, Balatsouras et al. (14) evidenced that cochlear injury may be present in patients with a normal PTA, pointing out the possibility of a subclinical dysfunction in subjects who do not complain about hearing problems.

Our study, for the first time, evaluated OHCs function through TEOAEs and DPOAEs, providing additional information about cochlear function in FSHD1. In fact, the use of both OAEs methods allowed us to study a larger spectrum of auditory frequencies and, through DPOAEs, to investigate subjects with mild-to-moderate hearing loss, which cannot be studied by TEOAEs (12). The reduction of OAEs with both methods and for all frequencies confirms that a global decrease in the cochlear function is a frequent and well-defined feature of FSHD1, even in those patients without hearing loss. Moreover, since results were not influenced by CAS, we could ascertain the integrity of the medial olivocochlear system, which is the central efferent pathway, in this type of hearing dysfunction. Discrepancies in the literature about the existence of hearing defects in FSHD1 could be attributable to subclinical hearing alterations not detectable by PTA examination, as highlighted by our study. Because of the aforementioned evidences, we think that a possible diagnosis of “hidden hearing loss” and/or cochlear synaptopathy (CS) in these patients should be also taken into consideration (21). In particular, hidden hearing loss represents a condition characterized by a neural alteration located at the level of the synapses between the inner hair cells and the auditory nerve, which is typically not detected by conventional audiometric evaluations, but only through particular Speech audiometry tests achieved in a “competing background noise” and other specific audiological assessments, including ABR (22).

Hearing alterations were detected also in patients with low-grade muscle burden or no signs of muscular involvement (FSHD clinical score ≤ 2), indicating that cochlear dysfunction occurs independently from muscle deterioration. This is confirmed by the lack of correlation between FSHD clinical score and cochlear abnormalities. We acknowledge that this finding may be affected by the small size of our cohort and by the clinical variability, which we observed between and even within families (23). A longitudinal study may help in clarifying whether the observed hearing alteration is progressive or not.

The absence of a clear genotype–phenotype correlation and the lack of an animal model closely resembling the human phenotype have so far limited understanding FSHD1 pathogenesis. However, existing evidence suggests that increased oxidative stress and mitochondrial dysfunction may contribute to tissue damage (24). Accordingly, the mis-expression of genes controlled by the D4Z4 repeat could lead to cochlear dysfunction by increasing susceptibility of hair cell to oxidative stress. Considering what has been described, it is tempting to speculate that SORBS-2, a gene highly expressed in OHC and regulated...
by D4Z4, may be involved in the pathophysiology of cochlear dysfunction in FSHD1 (25–27).

In conclusion, auditory impairment in FSHD1 patients seems to be linked to an alteration at cochlear level and may be detected even in those subjects with a normal PTA. Therefore, a complete audiological evaluation can provide useful information in all patients with genetically confirmed FSHD1 even if though no auditory symptoms are reported and when muscle involvement is subtle. Our study underlines the importance of evaluating hearing function in these patients not only by PTA but also with OAEs, a sensitive, cheap, noninvasive, and quantitative tool for the analysis of cochlear function. In particular, DPOAEs could be further investigated in larger cohorts and in longitudinal studies to assess their potential role as a marker of disease progression. Moreover, we think that a progression of this research with further audiological assessments, including ABR and speech audiometry tests realized in background noise, would be primary to understand more deeply the etiopathogenetic origin of auditory dysfunction in FSHD1 and may allow a better management and holistic approach to these patients.

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