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Short communication

An investigation of hearing impairment in de-novo Parkinson's disease patients: A preliminary study

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ABSTRACT

Objective: To investigate the peripheral auditory pathway in Parkinson's disease (PD) by using objective, quantitative and non-invasive audiological techniques, transient-evoked (TEOAE) and distortion product (DPOAE) otoacoustic emissions, in order to detect subclinical alterations of cochlear functioning and possible changes after dopaminergic stimulation.

Methods: We enrolled 11 untreated de-novo PD patients and 11 age and sex-matched healthy controls. Subjects underwent a routine audiological evaluation and otoacoustic emission recordings. The patients were then slowly-titrated to a stable dose of 100 mg levodopa four times in a day. A post-treatment assessment was made in order to detect significant changes in audiological responses. Finally, possible associations between clinical data and hearing results were also evaluated.

Results: At pure-tone audiometry, higher auditory threshold levels were observed in PD when compared to the controls. Moreover, DPOAE responses in PD patients were found low at almost all tested frequencies, suggesting subclinical cochlear damage. Interestingly, after dopaminergic treatment, a significant increase in DPOAE responses was detected. Notably, DPOAE dysfunction correlated with clinical severity, whereas high hearing thresholds appeared positively related with more prolonged disease duration.

Conclusions: Our findings demonstrate that otoacoustic emission recording and pure-tone audiometry reveal levodopa-sensitive cochlear dysfunction and hearing loss in PD. A parallel improvement in subjective motor symptoms and DPOAE objective responses could help clinicians in monitoring therapeutic responses and dynamic changes during the course of the disease.

1. Introduction

Hearing loss has recently been recognized as an additional non-motor feature in Parkinson's Disease (PD) [1]. Pathophysiological mechanisms underlying this hearing impairment are unclear, because contrasting results have been reported in previous studies [2]. A preferential impairment of pure-tones perception has been observed, suggesting a peripheral involvement as the basis of hearing loss in PD [1]. Interestingly, chemical neurotransmission in the organ of Corti resembles synaptic interplay already observed in basal ganglia. Glutamate and dopamine, released below inner hair cells (IHC), also play a key role in auditory neurotransmission and accurate perception of sounds (Esupp Figure 1) [3]. Notably, an excessive release of glutamate from IHC has been shown to induce an excitotoxic damage of primary auditory neurons [4]. Dopamine, which is released from lateral olivocochlear (LOC) efferent fibers below IHC, plays a significant modulating function on afferent

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dendrites, thus counteracting glutamate-excitotoxic effects [5]. Recent evidence of a possible otoprotective role of rasagiline, a MAO inhibitor commonly prescribed in PD, acting as a dopaminergic neurotransmission enhancer, provided support for this neuroprotective mechanism [6]. Another important auditory pathway preventing hearing damage is the cholinergic medial olivocochlear system (MOCS), which directly controls micromechanical activity of the outer hair cell (OHC), also located inside the organ of Corti [7].

Our study aimed to investigate the peripheral auditory pathway in PD *de-novo* patients firstly in a drug-free condition, then following dopaminergic stimulation by using objective, quantitative and non-invasive methods, transient-evoked (TEOAE) and distortion-product (DPOAE) otoacoustic emissions, to detect alterations of cochlear functioning and possible changes after dopaminergic treatment.

2. Patients and methods

We evaluated fifteen de-novo consecutive outpatients with idiopathic PD at the Movement Disorder Center of Policlinico Tor Vergata in Rome. To be considered eligible, patients were required to fulfill the following criteria: clinical diagnostic criteria for idiopathic PD, normal brain MRI scans, a dopamine transporter SPECT brain imaging that confirmed asymmetrical pre-synaptic dopaminergic deficit, no previous use of antiparkinson drugs, no cognitive impairment (MMSE > 26) and younger than 80 years. Exclusion criteria were: previous history of otological/labyrinthine disorders, exposure to excessive noise, ototoxic drug consumption and diabetes. A parallel group of eighteen subjects, consisting of healthy volunteers (CTRL) matched for age and sex with no history of otological and neurological disorders, was also included in our study.

At the time of enrollment, all subjects underwent a clinical and neurological evaluation that included the Unified Parkinson's Disease Rating Scale (UPDRS) part II-III and Hoehn &Yahr (H&Y) staging. A detailed clinical history of PD symptoms' onset was also obtained. To investigate the subjective perception of hearing disability in all the subjects, we used a self-report questionnaire [8] designed to provide information about any hearing problems in normal everyday life situations (Table 1). Before measuring audiometric pure-tone thresholds, an acoustic impedance test and otoscopic examination were performed in all subjects, in order to exclude possible middle ear diseases (e.g. otosclerosis, glue or tympanic perforation). Hearing loss was calculated for each pure-tone frequency stimulation (from 125 to 8000 Hz) separately as the amount of threshold shift above the standard audiometric zero. In the same session, TEOAEs and DPOAEs were also recorded in both ears of all subjects. TEOAEs and DPOAEs are low-level audio-frequency sounds produced in response to a click stimulus by the active micro-movements of OHC in the organ of Corti and simply detectable and measured from the external ear canal without requiring the patient's cooperation (Esupp Text) [9].

All eligible PD patients underwent all the evaluations twice: first, at baseline on no treatment, then in a stable chronic dopaminergic stimulation after a slow-titration of levodopa reaching a dose of 100 mg four times in a day within a time-span between one and three months depending on each subject's tolerance. All evaluations were made 1 h after the third daily dose of levodopa. All PD patients showed a clear cut motor improvement at the end of levodopa titration period otherwise they would have been excluded from the study. The controls only completed the baseline assessments. All subjects signed informed consent. Protocol was approved by the local Ethical Committee.

2.1. Statistical analysis

Audiometric data, given their non-normal distribution, were assessed separately by the Mann–Whitney test for multiple comparison and Wilcoxon test for repeated measures. Conversely, TEOAE and DPOAE measurements were compared first by MANOVA significance test due to co-linearity between OAE frequencies. In the event of significance, unpaired and paired t-tests were used for comparison between PD vs CTRL and PD before and after dopaminergic treatment; a *post-hoc* Bonferroni correction was applied considering statistically significant $p \leq 0.007$ for audiometry, $p \leq 0.01$ for TEOAE and $p \leq 0.008$ for DPOAE analysis. Correlations between audiological measurements and clinical data were assessed using parametric and non-parametric test as required. Statistical analysis was performed using SPSS version 17 (SPSS Inc., Chicago).

3. Results

Of the subjects, four PD patients and seven controls were not included in our data analysis: they had evidence of middle ear diseases during the otoscopic and/or acoustic impedance tests. The final sample consisted of eleven PD patients (mean age ±SD 66.5 ± 7.5 years; 8 males and 3 females) and eleven CTRL subjects (mean age ±SD 66.0 ± 8.8 years; 7 males and 4 females). The PD group, by history, showed a mean disease duration of 1.5 ± 1.3 years (range, 0.5–5.0 years) and, on clinical examination, a mean UPDRS III score of 23.5 ± 7.6 (range, 14–36). H&Y staging ranged from 1.5 to 2.5, with six subjects presenting with predominately left sided PD and five with predominantly right sided PD. All subjects completed audiological evaluations and data were recorded from both ears. All the measurements were used for data analysis. except for DPOAE data from one ear of a PD patient due to technical difficulties.

Otoscopic examination and acoustic impedance test, revealed that all subjects had intact ear drums and a type “A” (normal) tympanogram. Pure-tone audiometry revealed higher auditory

Table 1
Demographic and clinical data of PD patients and controls.

	PD group (n = 11)	CTRL group (n = 11)	Sig.
Age (years)	66.5 ± 7.5	66.0 ± 8.8	n.s.
Sex (male/female)	8/3	7/4	n.s.
Time from first PD symptom (years)	1.5 ± 1.3	–	–
UPDRS II score	7.6 ± 3.7	–	–
UPDRS III score	23.5 ± 7.6	–	–
H&Y stage	2.0 ± 0.4	–	–
Most PD affected side (Left/Right)	6/5	–	–
Subjective auditory disability (raw score)	22.8 ± 8.3	21.8 ± 7.1	n.s.

Note: Clinical data in the table are expressed as mean ± SD. PD, Parkinson's disease; CTRL, control group of healthy subjects; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn-Yahr.

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