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Olfactory and gustatory dysfunction in Myasthenia gravis: A study in Turkish patients

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ABSTRACT

Objective: Myasthenia gravis (MG) is commonly viewed as a muscle disorder. Less is known about neurosensory function and dysfunction in MG. We aim to evaluate olfactory and gustatory behavior in Turkish patients with MG, and compare these results with age and sex-matched healthy controls.
Material/methods: 30 individuals with MG, and 30 healthy volunteers were studied. Olfactory function was studied with the Sniffin' sticks test. Taste strip test was used for studying taste function. The t-test was used for analyzing continuous variables, and the chi-square test for categorical data. Clinical staging and medication status were included in a model analyzed using analysis of variances.
Results: MG patients showed significantly lower olfactory ($p < 0.001$) and gustatory scores ($p < 0.001$) than the healthy controls. In addition, olfactory loss correlated with the severity of the disease. Medications for MG did not influence these results.
Conclusion: This study replicates the olfactory dysfunction found elsewhere in MG. Further, gustatory dysfunction, an activity unrelated to muscle strength, was also unveiled. Medications used for treating MG must not be blamed for the chemosensory dysfunction found in this neurological disorder.

1. Introduction

Stimulation of a peripheral nerve results in the release of acetylcholine (ACh) molecules at the neuromuscular junction (NMJ). These molecules bind to a number of receptors located on the striated muscle, resulting in the depolarization of the postsynaptic muscle membrane, generating a muscle contraction [1]. When this complex machinery fails, neural disorders appear. Myasthenia gravis (MG) is one of the prototypes of such disorders. MG is an autoimmune disease that classically damages the transduction of signals on the postsynaptic cell membrane, affecting the function of the NMJ [2]. Antibodies against nicotinic acetylcholine receptors have been found in about 85% of patients with MG [3,4]. Fluctuating muscle weakness and fatigue are the classical signs and symptoms in MG [5]. Sensory complaints, including smell or taste, are not commonly and quantitatively studied in MG [6].

Chemosensory function plays a significant role in environmental and nutritional safety, as well as in the quality and enjoyment of life. Complex neural pathways, not well understood, are involved in chemosensation modulation. In brief, olfactory neurons are situated in the nasal mucosa, at the upper third of the nasal cavity [7]; their axons connect with the dendrites of glomeruli in the olfactory bulb. Odors binding to the olfactory receptor neurons trigger olfactory activity [8]. The processing of odors within the central nervous system includes the orbitofrontal cortex, the limbic system, insula and cerebellum, among other structures [9,10]. Gustatory fibers, on the other hand, reach the brain via the facial, glossopharyngeal, and vagal nerves. These nerves send the afferent impulses to the nucleus tractus solitarii, central tegmentum, posteromedial ventral thalamic nucleus and anterior insula and the orbitofrontal cortex [11].

Gender and age influence smell and taste function [12]. Men show lower scores of smell function than women [13]. Smell loss correlates stronger than taste loss with aging [14]. Smell can also be affected by environmental factors such as airborne pollution and toxic odors [15],

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head trauma [16], as well as rhinitis and allergies [17]. Taste can be reduced by middle ear infections [18], medications [19], chemotherapy and radiation, among other cofactors [20–22]. Olfactory and gustatory disturbances have also been found to be key early markers of neurodegenerative disorders. Alzheimer's disease (AD) and Parkinson's disease (PD) are the prototype of these [22] neural disorders [23–25], suggesting that chemosensory disorders in AD and PD may originate in altered acetylcholine mechanisms [23–25].

Importantly, Leon-Sarmiento et al. discovered that individuals with MG, a unique disorder with pure dysfunctional Ach neural transmission, had smell disorders as measured by the University of Pennsylvania Smell Identification Test (UPSIT) [26]. These authors reported that the UPSIT scores in patients with MG were similar to scores reported from the above-mentioned neurodegenerative diseases [26]. However, no gustatory function was investigated in Leon-Sarmiento et al.'s study [26].

We aim to replicate the olfactory anomalies reported by Leon-Sarmiento et al. in MG [28] using the Sniff and Stick test. We also aim to expand chemosensory research in MG, and study gustatory function in the same group of patients. The results of this study confirm that MG patients have, in fact, olfactory dysfunction; moreover, it is demonstrated here that taste dysfunction is also present in MG. Altogether, these studies point out a global chemosensory dysfunction in a neurological syndrome disorder classically viewed as a muscle-related disorder.

2. Material and methods

2.1. Subjects

30 MG patients (22 men, 8 women) were studied. The mean age of patients was 38.7 ± 13.2 years.

The age- and sex-matched control group consisted of 30 healthy individuals (22 men, 8 women), who had a mean age of 38.9 ± 13.1 years. Each participant underwent clinical evaluation, which included general, otorhinolaryngology and cardiovascular evaluations. Past and current olfactory and gustatory functions were questioned. The mini mental state examination (MMSE) was applied. Since smell and taste are negatively correlated to cognitive impairment [23–25], only MG patients who scored ≥28 in the MMSE were included in the study. Similarly, patients who obtained ≤2 points in the expanded disability status scale, a test that assesses general functional status [27], was included. A comprehensive questionnaire was applied to patients and healthy controls to assess socio-demographic and toxicological information, medication status, past oronasal surgery, and educational level. Individuals wearing dentures or with a history of alcoholism, drug abuse, cardiovascular disease, major psychiatric and/or neurological disorders, coated tongue, poor oral health, nasal surgery, basilar skull fracture, head trauma, HIV positive status, or any rhinological pathology were excluded. Chest X-ray was done to rule out thymoma.

2.2. Assessment of MG patients

MG diagnosis was made by a trained neuromuscular neurologist. Participants were evaluated according to the Myasthenia Gravis Foundation of America Clinical Classification System [28]. The clinical impression was confirmed by a positive edrophonium ("Tensilon") test and classical electrodiagnostic findings [29].

2.3. Chemosensory assessment

2.3.1. Olfactory function

Psychophysical testing of olfactory function was performed with the Sniffin' sticks test, validated for the Turkish population [30–33]. Odorants were presented in felt-tip pens ("Sniffin' sticks"; Burghart GmbH, Wedel, Germany) [30–33]. Olfactory testing comprised of three tests, namely tests for odor threshold (testing by means of a single staircase procedure), odor discrimination (3-alternative forced choice [AFC]) and odor identification (4-AFC). For odor presentation, a pen's cap was removed by the experimenter for approximately 3 s and the tip of the pen was placed approximately 1–2 cm in front of the nostrils.

Odors were presented in a total of 16 triplets of pens: one pen containing diluted phenyl ethyl alcohol and two containing propylene glycol, which served as blanks. The interval between presentations of individual pens of a triplet was approximately 3 s; presentation of the triplets was every 20 s. With the 3-AFC paradigm, subjects had to identify the pen that contained the odorant. Subjects were blindfolded to prevent visual identification of the odor containing pens. Thresholds of odor were determined using a single staircase technique. Two successive correct identifications of the pen containing the odor or one incorrect identification triggered a reversal of the staircase to the next higher or the next lower dilution step, respectively. The odor thresholds were determined as the mean of the last 4 from a total of 7 staircase reversals [30–33].

For odor discrimination 16 triplets of pens were presented, with two containing the same odorant and one containing the target odorant. The subjects' task was to identify the sample that had a different smell. Participants were also blindfolded. Presentation of triplets was separated by at least 30 s. The result was a sum score of correctly identified pens.

Lastly, odor identification was performed for 16 common odors. Identification of individual odors was performed from a list of four verbal descriptors each. The experimenter presented each odorant in intervals of at least 30 s to minimize olfactory desensitization. Subjects were free to sample the odors as often as necessary to make a decision. The test result named as the threshold discrimination identification score (TDI) was the sum score of the correctly identified odors [30–33].

2.3.2. Gustatory function

The taste test was based on filter paper strips ("Taste Strips", Burghart, Wedel, Germany) [34]. The strips had a length of 8 cm and a tip area of 2 cm^2 being impregnated with tastant (4 concentrations of each of the 4 basic taste qualities) [21,34]. The strips were placed on the middle of the anterior third of the tongue, resulting in a total of 16 trials. Participants were allowed to suck on the strip for a maximum of 20 s. Before each administration of a strip, the mouth was rinsed with water. The tastes were presented in increasing concentrations. Taste qualities were applied randomly at each of the four levels of concentration. Participants had to identify the taste from a list of four descriptors, i.e. sweet, sour, salty, and bitter. The number of correctly identified tastes was added up to a "taste score" [21,34].

2.4. Statistical analyses

Data analysis was made using the Statistical Package for the Social Sciences (SPSS), version 21 (SPSS Inc., Chicago, Ill. USA). A model using one-way analyses of variance (ANOVA) was implemented. Olfactory tests were compared between groups, with "olfactory test" as within subject factor, and "group" as subject factor. Gustatory tests were analyzed with "side of testing" and "taste quality" as within-subject factor, and "group" as between-subject factor. The t-test was used for continuous variables. Correlations were calculated using the Pearson test. P value was set at <0.05. Results from olfactory testing can be analyzed separately from each other and/or as the sum of the scores from the three individual tests [32,35]. Since our aim was to determine olfactory and gustatory dysfunction, collapsed olfactory analyses were not done.