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Transient impairment of olfactory threshold in acute multiple sclerosis relapse

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ABSTRACT

Background: Impairment of olfactory threshold is a feature of early and active relapsing remitting multiple sclerosis (RRMS). It predicts inflammatory disease activity and was reported to be transient. However, the timing of onset and resolve of olfactory threshold impairment remains unclear.

Objective: To prospectively assess the development of olfactory threshold in acute MS relapse over time in comparison to stable MS patients.

Methods: In a prospective observational design, we measured olfactory threshold by performing the Sniffin' Sticks test (minimum score 0, maximum score 16 reflecting optimal olfactory function) at baseline and after 4, 12 and 24 weeks. We included 30 RRMS patients with acute MS relapse and 30 clinically stable RRMS patients (defined as no relapse within the last 12 months) as a control group.

Results: Olfactory threshold was impaired in patients with acute MS relapse at baseline (median difference = −3.5; inter-quartile range [IQR] −4.5– −2.5; $p < 0.001$), week 4 (−2.5; IQR −3.0 – −2.0; $p < 0.001$), week 12 (−1.5; IQR −2.0 – −0.5; $p = 0.002$) and week 24 (−0.5; IQR −1.0 – 0.0; $p = 0.159$) compared to stable MS patients. Of note, in relapsing patients in whom disease-modifying treatment was initiated or escalated after relapse, threshold did not differ anymore from stable patients at week 12 (−0.5; IQR −1.0 – 0.5; $p = 0.247$) and week 24 (0.0; IQR −1.0 – 1.0; $p = 0.753$).

Conclusions: Olfactory threshold impairment seems to be a transient bystander feature of MS relapse. It may be correlated to the level of inflammation within the CNS and might be a useful biomarker in this regard.

1. Introduction

Dysfunction of different qualities of the olfactory sense is increasingly recognized in multiple sclerosis (MS) (Doty et al., 1997, 1998,1999; Hawkes et al., 1997; Zivadinov et al., 1999; Zorzon et al., 2000).

The capacity to correctly identify odors (identification) and discriminate them (discrimination) is stronger affected in progressive and more advanced MS and slowly deteriorates over time in patients suffering further disability progression (Lutterotti et al., 2011; Erb et al., 2012; Rolet et al., 2013; Erb-Eigner et al., 2014; Bsteh et al., 2017).

Olfactory threshold is altered in early, active multiple sclerosis and predicts short term inflammatory disease activity (Lutterotti et al., 2011; Bsteh et al., 2017). Impairment of threshold appears to be transient resolving in the absence of inflammatory disease activity (Bsteh et al., 2017).

Olfactory threshold has been suggested to be a function of more peripheral parts of the olfactory system ("cable function") which might be more affected by inflammatory processes rather than by brain atrophy (Shoenfeld et al., 2009; Shoenfeld, 2007; Atanasova et al., 2008; Martzke et al., 1997). The transient nature of threshold impairment compared to the irreversible affection of discrimination and identification strengthens the plausibility of this concept.

However, these observations are based on studies applying testing intervals of 12 months. Therefore, the short-term dynamics of olfactory threshold impairment over time, especially regarding the timing of its onset and resolve in the context of acute inflammatory activity are entirely unclear.

Therefore, we aimed to prospectively assess the development of olfactory threshold in acute MS relapse over time in comparison to stable MS patients.

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2. Methods

In this prospective observational study, we included 30 relapsing remitting MS (RRMS) patients with acute MS relapse and 30 clinically stable RRMS patients as a control group. Patients were recruited from the MS outpatient clinic of the Clinical Department of Neurology at the Medical University Innsbruck. The study was approved by the ethics committee of the Medical University Innsbruck (ethical approval number: AM3743-281/4.3) and all participants gave written informed consent before inclusion.

MS patients were diagnosed according to the 2010 McDonald's criteria (Polman et al., 2011). Patients had to be aged between 18 und 55 years. A relapse was defined as symptoms with objectively observed neurological signs typical of an acute CNS inflammatory demyelinating event with duration of at least 24 h in the absence of fever or infection, separated from the last relapse by at least 30 days (Poser et al., 1983). Every relapse was treated with a single course of intravenously applied high dose methylprednisolone (4000 mg over 5 days) without oral tapering. For inclusion in the study, the onset of relapse symptoms had to occur not longer than 7 days prior to baseline.

Clinically stable MS was defined as absence of relapse for at least 12 months prior to inclusion in the study. All patients included had to be either treated with a single disease modifying therapy (DMT) or be without DMT for at least 6 months prior to baseline.

Patients were excluded, if they suffered a separate relapse or received an additional course of corticosteroids during the observation period. Other exclusion criteria were severe cognitive impairment defined as a score of 23 or lower in the Mini Mental State Examination (MMSE), or a history of chronic oto-rhino-laryngeal (ORL) disease (such as chronic rhinitis, nasal polyposis or sinus disease), head trauma, toxic exposures, upper respiratory infections at the time of assessment, previous radiation, nasal and/or oral surgery, symptoms of nasal obstruction or other neurological diseases known to be associated with olfactory disturbances.

Study visits were conducted at baseline and after 4 (W4), 12 (W12) and 24 (W24) weeks of follow up. A structured questionnaire regarding demographic data, smoking habits, neurological and pharmacological history including DMT, subjective olfactory function and use of drugs and hormonal contraceptives was obtained from each participant at every visit. Expanded disability status scale (EDSS) was obtained at every visit (Kurtzke, 1983).

The Beck Depression Inventory (BDI), was performed at each visit to screen for depression. Depression was defined as a score of 18 or higher on the BDI (Steer et al., 1999).

Olfactory threshold was assessed at each visit using the first stage of the extended version of the Sniffin' Sticks test (Burghart Medizintechnik, Wedel, Germany) according to the manufacturer's instruction including change of testing sticks every six months (Hummel et al., 2007; Rumeau et al., 2016). The Sniffin´ Sticks test is based on pen-like odor-dispensing devices. Olfactory threshold is assessed using n-butanol as a single odorant. Three sticks are presented to each subject in a randomized order, two containing solvent and the third containing the odorant at a certain dilution. The subject is asked to identify the stick with the odorant. The threshold score was rated for each patient at every visit. The maximum score is 16 points and reflects optimal olfactory threshold. Lower scores are associated with an increased threshold for odor perception. The normative values are based on data from 3000 healthy subjects (Hummel et al., 2007). The investigator performing the olfactory testing was blinded for clinical information including relapse status. Olfactory testing was postponed for 1 week if the patient had upper respiratory tract infection at the time of assessment.

2.1. Statistics

Statistical analysis was performed using SPSS 24.0 (SPSS Inc, Chicago, IL). Categorical variables were expressed in frequencies and percentages. Continuous variables were tested for normal-distribution by the Kolmogorow–Smirnow test. In case of normal-distribution variables were displayed as mean and standard deviation or 95% confidence interval. If variables were not normally distributed, they were displayed as median and inter-quartile range (IQR). Univariate comparisons were done by Chi-square-test, Mann-Whitney U test and independent *t*-test as appropriate. Comparisons of olfactory threshold at different points of time were done by Friedman test.

Table 1
Demographic and clinical characteristics of RRMS patients at baseline.

	Relapse group (n = 28)	Stable group (n = 27)	p-value
Female[a]	20 (71.4)	21 (77.7)	0.829[d]
Age[b]	34.6 (8.4)	33.7 (9.0)	0.702[e]
EDSS[c]	2.0 (0 – 6.5)	1.5 (0 – 6.5)	0.613[f]
DMT received at baseline[a]	19 (67.9)	20 (74.1)	0.786[d]
Current DMT at baseline			
Interferon beta[a]	5 (17.9)	6 (22.2)	
Glatirameracetate[a]	5 (17.9)	5 (18.5)	
Dimethylfumarate[a]	6 (21.4)	7 (25.9)	
Teriflunomide[a]	1 (3.6)	1 (3.7)	
Fingolimod[a]	2 (7.1)	1 (3.7)	
Beck-Depression Index[b]	5.0 (5.3)	4.3 (5.1)	0.620[e]
Depression (BDI ≥ 18)[a]	1 (3.6)	2 (7.4)	0.531[d]
MMSE[c]	30 (27 – 30)	30 (27 – 30)	0.999[f]
Smokers[a]	9 (32.1)	9 (33.3)	0.902[d]
Number of cigarettes per day[b]	4.4 (8.0)	4.0 (7.8)	0.851[e]

MS… relapsing-remitting multiple sclerosis; EDSS…expanded disability status scale; DMT…disease modifying therapy; BDI…Beck-Depression Index; MMSE… mini-mental status examination.
[a] number (percentage).
[b] mean and standard deviation.
[c] median and range.
[d] Chi-square test.
[e] independent *t*-test.
[f] Mann–Whitney-U test.

3. Results

Characteristics of patients at baseline are given in Table 1. 28/30 (93.3%) patients in the relapse group and 27/30 (90%) in the clinically stable group completed the study, respectively. Two patients were excluded because they suffered a separate relapse during the observation period, two had to be excluded because they received an additional course of corticosteroids and one patient was lost to follow up.

Olfactory threshold was impaired in patients with acute MS relapse at baseline (median difference = −3.5; inter-quartile rang [IQR] −4.5 – −2.5; $p < 0.001$), week 4 (−2.5; IQR −3.0 – −2.0; $p < 0.001$), week 12 (−1.5; IQR −2.0 – −0.5; $p = 0.002$) and week 24 (−0.5; IQR −1.0 – 0.0; $p = 0.159$) compared to stable MS patients. Threshold scores did not change in clinically stable patients. (Fig. 1)

We did not find a difference in olfactory threshold impairment when

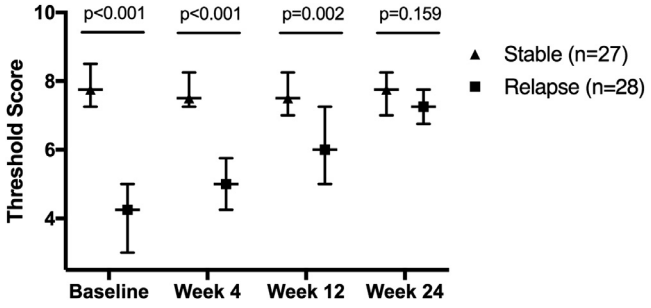

Fig. 1. Olfactory threshold in relapsing and stable MS patients over 24 weeks.