Olfactory Dysfunction Reflects Disease Progression in Japanese Patients with Multiple Sclerosis

Kazumasa Okada¹, Shingo Kakeda² and Masayuki Tahara³

Abstract:
Objective  Olfactory dysfunction is an important clinical feature in patients with multiple sclerosis (MS). The incidence and extent of olfactory dysfunction are reportedly higher in secondary progressive (SP) MS than in relapsing and remitting (RR) MS. We investigated the use of olfactory dysfunction for evaluating the disease status of Japanese patients with MS.

Methods  Olfactory identification was evaluated using the Odor Stick Identification Test for the Japanese (OSIT-J) in patients with RRMS (n=40) and SPMS (n=11) and compared the findings with those of healthy controls (n=40). Patients with RRMS for more than 10 years (L-RRMS, n=10) were included in the RRMS group. The cognitive function was evaluated using the Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition. The third ventricle width (3rd VW) was measured as a marker of central brain atrophy using magnetic resonance imaging.

Results  SPMS patients had significantly lower OSIT-J scores than RRMS and L-RRMS patients. More SPMS patients had OSIT-J scores below the lower limit of the normal score (LLN) than RRMS patients. The LLN effectively discriminated between RRMS and SPMS (sensitivity 70%, specificity 91.5%, area under the curve 0.933, 95% confidence interval 0.874-1.000). Patients with SPMS had a significantly lower processing speed and larger 3rd VW than those with RRMS or L-RRMS.

Conclusion  The olfactory dysfunction was worse, along with cognitive impairment and brain atrophy, in SPMS patients than in RRMS patients, independent of disease duration, in our Japanese population. This directly reflected the disease progression and may have been able to distinguish SPMS from RRMS, independent of ethnic and cultural background.

Key words: olfactory dysfunction, relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, cognitive impairment, brain atrophy

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Introduction

Olfactory dysfunction is an important clinical feature and common symptom in multiple sclerosis (MS) patients with cognitive impairment (1, 2). Approximately 11-67% of MS patients exhibit olfactory dysfunction in the course of their disease. The incidence of olfactory dysfunction is dispersed due to diversity in the olfactory test used and variability of MS patients included in each study (1-3). In addition, recent studies have shown that olfactory dysfunction is associated with functional disability and cognitive impairment and negatively affects daily activity and the quality of life (4-7). Consequently, olfactory evaluations are crucial in the clinical practice of MS.

Odor perception uses different brain areas involving the olfactory cortex (e.g. anterior olfactory nucleus, olfactory tubercle, piriform cortex, amygdala, and rostral entorhinal cortex) and areas of higher brain functions, such as learning, memory, and emotion. These areas include the orbitofrontal...
cortex, perirhinal cortex, insula, amygdala, hippocampus, striatum, and thalamus (8, 9). The pathological hallmarks of MS, such as diffuse inflammatory and neurodegenerative changes, also affect both the olfactory cortex and its associated brain areas, resulting in olfactory dysfunction in MS patients (10, 11). Using diffusor tensor imaging in MS patients, Erb et al. showed that impairment in olfactory identification was correlated with damage to the olfactory cortex (12). Bsteh et al. also reported that impaired olfactory identification and discrimination, involving the olfactory cortex, was associated with gray matter atrophy of the anterior cingulum, mesial temporal region, and basal frontal region, among MS patients (13).

Bsteh et al. reported that the combination of identification and discrimination in the Sniffin’ Sticks test was correlated with persistently elevated levels of serum neurofilament light chains (14), which reflected the neurodegenerative process. In addition, olfactory dysfunction is more prevalent in secondary progressive MS (SPMS) patients than in relapsing and remitting MS (RRMS) patients, and olfactory identification is worse in patients with SPMS than in those with RRMS (5, 15). We previously reported that impaired olfactory identification is correlated with the cognitive function, Expanded Disability Status Scale (EDSS), and central brain atrophy in RRMS patients (6). These results suggest that impairment of olfactory function, especially olfactory identification, is a potential marker for disease progression of MS.

We therefore investigated the relationship between olfactory dysfunction and other disease status markers, including cognitive dysfunction, functional disability, and central brain atrophy, in SPMS and RRMS to elucidate the utility of olfactory dysfunction as a disease progression marker for Japanese patients with MS.

Materials and Methods

Participants

This study included 51 consecutive Japanese patients with MS (40 with RRMS and 11 with SPMS) who met the 2010 McDonald diagnostic criteria from the outpatient clinic of the Department of Neurology of the University of Occupational and Environmental Health and 40 healthy controls (HC) (16). All patients with RRMS, except for two, and all HCs had participated in our previous study (6). Patients with SPMS were defined according to the proposed definition: initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remission, and plateaus (17). The exclusion criteria included age below 18 or above 65 years old, a clinical relapse within 3 months before testing or ongoing corticosteroid treatment, a history of chronic otorhinolaryngeal diseases (such as chronic rhinitis, nasal polyposis, or sinus disease), head trauma, a history of nasal or oral surgery, symptoms of nasal obstruction, the presence of other neurological diseases such as Parkinson’s disease and Alzheimer’s disease, or the presence of other medical conditions associated with olfactory disturbances. We also excluded patients and HCs who had a depressive state according to the Center for Epidemiologic Studies Depression Scale (score more than 16 points) and those who were current smokers (18). No patients showed nasal abnormalities on magnetic resonance imaging (MRI).

The study was approved by the ethics committee of the University of Occupational and Environmental Health. All participants provided their written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

The assessment of the neurological and cognitive function

All MS patients were evaluated during a period without disease activities based on clinical and MRI examinations. Neurological and olfactory examinations were performed at the same time. The Japanese version of the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) was used to assess the cognitive function (19). The WAIS-III evaluated the full-scale Intelligence Quotient (FIQ), verbal IQ (VIQ), and performance IQ (PIQ) scores, as well as the index scores of processing speed (PS), working memory (WM), perceptual organization (PO), and verbal comprehension (VC). This was done using 14 subtests according to the standardized instructions of the manual. The index scores were used to clarify which cognitive modality was associated with the disease progression of MS in this study. We confirmed that the index scores evaluated the cognitive function and were associated with central brain atrophy in RRMS (6, 20). Other detailed clinical information on the patients was collected from the patients’ charts.

Olfactory examinations

The Odor Stick Identification Test for Japanese (OSIT-J; Daiichi Yakuhin Sangyo, Tokyo, Japan) was used to assess olfactory identification (6). This test, which included 12 odorants familiar to the Japanese population (perfume, rose, condensed milk, Japanese orange, curry, roasted garlic, fermented beans/sweaty socks, gas for cooker, menthol, India ink, wood, and Japanese cypress), was similar to the Brief Smell Identification Test (B-SIT), which included 12 items to evaluate olfactory identification (21). The total number of correct answers was recorded as the OSIT-J score. The participants were directed to avoid eating 10 minutes before the evaluation. Hyposmia was defined as an OSIT-J score of ≤8 points (22).

MRI data acquisition and third ventricle width (3rd VW) measurement

All MRI studies were performed using a Signa Excite 3T scanner (GE Healthcare, Milwaukee, USA) and a dedicated 8-channel phased array coil (USA Instruments, Aurora, USA). The imaging parameters for fluid-attenuated inversion recovery (FLAIR) imaging were 12,000/140/2,600/1/9.1/2 minutes and 36 seconds (repetition time ms/echo time ms/
Table 1. Characteristics of Participants.

|                | RRMS | L-RRMS | SPMS | HC |
|----------------|------|--------|------|----|
| Number         | 40   | 10     | 11   | 40 |
| Female n=32 (80%) | n=9 (90%) | n=9 (75%) | n=32 (80%) |
| Age, years     | 38 (20-64) | 43.5 (29-52) | 39.5 (25-60) | 35 (24-61) |
| Age at onset, years | 33 (13-43) | 31 (18-38) | 33 (15-48) | - |
| Duration, years | 3.5 (1-24) | 13 (10-24) | 12 (9-17)** | - |
| Total number of attacks | 3 (2-6) | 3 (2-6) | 5 (3-9)** § | - |
| EDSS (median, range) | 1.0 (0-3.0) | 2.0 (1.0-3.0) | 6.0 (3.0-6.5)* § | - |
| Smoking        | None | None | None | None |
| OCB positivity n=37 (92.5%) | n=9 (90%) | n=11 (100%) | - |
| CES-D (median, range) | 10 (2-12) | 8 (4-10) | 11 (6-13) | - |
| Patients on DMT n=38 (95%) | n=10 (100%) | n=11 (100%) | - |
| IFN-β1a n=6 (15%) | n=2 (20%) | n=0 (0%) | - |
| IFN-β1b n=2 (5%) | n=0 (0%) | n=0 (0%) | - |
| Dimethyl fumarate n=18 (45%) | n=7 (70%) | n=4 (36.3%) | - |
| Fingolimod n=7 (17.5%) | n=1 (10%) | n=5 (45.5%) | - |
| Natalizumab n=5 (12.5%) | n=0 (0%) | n=2 (18.2%) | - |

Values shown are median (range). EDSS: Expanded Disability Status Scale, OCB: oligoclonal band, CES-D: center for epidemiologic studies depression scale, DMT: disease modifying therapy, IFN: interferon. RRMS vs. SPMS *p<0.05, **p<0.01, L-RRMS vs. SPMS §p<0.05, #p<0.01.

Results

A total of 40 RRMS and 11 SPMS patients as well as 40 HCs were included in this study. The clinical characteristics of the MS and HC patients are presented in Table 1. The proportion of women was higher among RRMS patients than among SPMS patients. Both patient groups were matched for age. There were significant differences between the RRMS and SPMS patients in terms of the disease duration, EDSS, and the number of relapses. We also compared the RRMS patients with a disease duration of more than 10 years (L-RRMS patients, n=10) and the SPMS patients to investigate the impact of the disease duration. The SPMS patients had a higher EDSS and more frequent relapses than the RRMS patients.

The OSIT-J scores were lower in the RRMS (median 10, range 8-12) and SPMS patients (median 8, range 6-9) than in the HCs (median 12, range 10-12) (Fig. 1). The RRMS patients had a significantly lower score than the RRMS and L-RRMS patients (median 8, 72.7%) than in RRMS (n=4, 10%) (p=0.004) and L-RRMS patients (n=1, 10%) (p=0.043). No patients had hyposmia in the HC group. An ROC analysis determined the threshold score to be 8, which is also the threshold score for hyposmia, to discriminate SPMS from RRMS [sensitivity 70%, specificity 91.5%, area under the curve (AUC) 0.933, 95% confidence interval (CI) 0.874-1.000].

The secondary indices of WAIS-III (VC, PO, WM, PS) and 3rd VW were compared among the MS groups. Although there was no marked difference in the VC, PO, or WM between the RRMS, L-RRMS, and SPMS groups, the PS was significantly lower in the SPMS patients (median 67, range 50-105) than in the RRMS (median 91, range 55-127) and L-RRMS patients (median 82, range 60-127) (Fig. 2). There was no marked difference in the PS between the RRMS and L-RRMS patients. The 3rd VW was significantly larger in the SPMS patients (median 8.20 mm, range 5.2-10.3) than in the RRMS (median 3.87 mm, range 2.2-9.5) and L-RRMS patients (median 5.33 mm, range 2.25-9.5) (Fig. 3). There was no marked difference in the 3rd VW between the RRMS and L-RRMS patients.

In addition, we classified all MS patients, including the RRMS and SPMS patients (n=51), into two groups based on the OSIT-J threshold score of 8 points and compared the groups. MS patients with an OSIT-J score ≤8 (n=13, OSIT-J score; median 8, range 6-8) had a longer disease duration,
Figure 1. The comparison of olfactory identification. The olfactory identification score was significantly lower in RRMS, L-RRMS, and SPMS patients than in HCs. *p<0.05, **p<0.01. HC: healthy control, L-RRMS: RRMS with disease duration longer than 10 years, OSIT-J: Odor Stick Identification Test for the Japanese, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS.

Figure 2. The comparison of the cognitive function. *p<0.05. L-RRMS: RRMS with disease duration longer than 10 years, PO: perceptual organization, PS: processing speed, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS, VC: verbal comprehension, WM: working memory.

Figure 3. The comparison of central brain atrophy. p<0.01 vs. RRMS and L-RRMS. 3rd VW: third ventricular width, L-RRMS: RRMS with disease duration longer than 10 years, RRMS: relapsing-remitting multiple sclerosis, SPMS: secondary progressive MS.

Discussion

We evaluated and compared the olfactory identification abilities of RRMS and SPMS patients with those of individuals in the HC group. Both RRMS and SPMS patients had a lower score for olfactory identification than the HCs. In addition, hyposmia was present in some patients with MS (RRMS: 10%, SPMS: 72.7%), but not in the HC group. The results are in line with previous studies, which reported that impairment of olfactory identification was a cardinal symptom of MS and occurred more frequently in SPMS patients than in RRMS patients (5, 15). We also found that olfactory identification was significantly associated with disability and brain atrophy, which are recognized as disease progression markers, in all MS patients. In addition, SPMS patients had a significantly lower score for olfactory identification than RRMS patients, and the prevalence of hyposmia was significantly higher in SPMS patients (72.7%) than in RRMS patients (10%). Thus, impairment of olfactory identification is thought to worsen in association with disease progression.

We compared olfactory identification between SPMS patients, who have had the disease for up to 9 years, and L-RRMS patients, who have had the disease for 10 years or more, in order to investigate the effect of disease duration on olfactory identification. Despite having the disease for a longer period, the identification abilities of L-RRMS patients were similar to those of other RRMS patients. In contrast, SPMS patients had a significantly lower score for olfactory identification and higher incidence of olfactory identification impairment than L-RRMS patients, despite no significant difference in the disease duration, age at the disease onset, or age at the olfactory identification examination. The results indicate that impairment of olfactory identification was related to the pathological progression of MS, inde-
The comparison between hyposmic and normosmic patients with multiple sclerosis. *p<0.05, **p<0.01. L-OSIT: hyposmic patients with OSIT-J score ≤8 (n=13), N-OSIT: normosmic patients with OSIT-J score >8 (n=38), 3rd VW: third ventricular width, EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, OSIT-J: Odor Stick Identification Test for the Japanese, PO: perceptual organization, PS: processing speed, VC: verbal comprehension, WM: working memory

Table 2. Spearman’s Rank Correlation Coefficient.

|                          | Age  | Disease duration | Attack numbers | EDSS  | 3rd VW | PO    | VC    | WM    | PS    |
|--------------------------|------|------------------|----------------|-------|--------|-------|-------|-------|-------|
| **Whole MS**             | -0.233* | -0.681**         | -0.302*        | -0.365** | -0.527** | 0.201 | 0.203 | 0.255* | 0.288* |
| **RRMS**                 | -0.283 | -0.324*          | -0.228         | -0.354* | -0.746** | 0.348 | 0.302 | 0.444* | 0.522** |
| **L-RRMS**               | -0.256 | -0.1             | -0.366         | 0.062  | -0.395  | -0.134 | 0.299 | 0.277  | 0.329  |
| **SPMS**                 | -0.101 | -0.429           | -0.083         | -0.618 | -0.343  | 0.101 | 0.151 | 0.091  | 0.061  |

OSIT-J: Odor Stick Identification Test for the Japanese, EDSS: Expanded Disability Status Scale, 3rd VW: third ventricular width, VC: verbal comprehension, PO: perceptual organization, WM: working memory, PS: processing speed. *p<0.05, **p<0.001.

**Figure 4.** The comparison between hyposmic and normosmic patients with multiple sclerosis. However, impairment of olfactory identification was associated with the disease duration only in RRMS patients but not in SPMS and L-RRMS. The results suggest that although the olfactory identification ability may start to decline over time, reflecting the pathological change in disease progression during RRMS (14), olfactory identification ability may worsen inconsistently or be preserved during the disease course. Moreover, the variation of olfactory identification seems to be different in each patient as the trajectory of the disease progression is various for each patient with RRMS (24). In contrast, olfactory identification may become impaired in RRMS patients transitioning into SPMS.

In addition to low olfactory identification, SPMS patients had a significantly wider 3rd VW and a lower PS score on WAIS-III than RRMS or L-RRMS patients. PS is an important aspect of the cognitive function in patients with MS, which is more frequently impaired in SPMS patients than in RRMS patients (25, 26). Previous studies have also shown that olfactory identification was worse in SPMS patients.
than in RRMS patients and was associated with cognitive dysfunction (4, 15). Furthermore, 3rd VW has been shown to be a good indicator of cognitive status, especially PS, in both RRMS and SPMS patients (23, 27). These results support the notion that olfactory identification has potential prognostic value to predict future cognitive impairment, which greatly reflects MS progression, causes functional disability, and seriously impacts patients’ quality of life. In the present study, olfactory identification did not correlate with the 3rd VW or cognitive function in SPMS patients, although the associations were significant in RRMS patients. We speculate that olfactory identification may gradually worsen over the course of RRMS along with cognitive dysfunction and brain atrophy and may become evident during its transition to SPMS. However, the worsening of the olfactory identification ability is probably too slow to be captured by the OSIT-J after transitioning to SPMS. Another explanation is that the olfactory identification ability might not worsen for a certain period of time after the conversion of RRMS to SPMS, as we did not note any SPMS patients with anosmia in this study.

The utility of the OSIT-J to discriminate between SPMS and RRMS was also evaluated by an ROC analysis in this study. The RRMS and SPMS patients were separated by an OSIT-J threshold score of 8 points, which indicates hyposmia. Similarly, in the study of all MS patients, those with an OSIT-J score of ≤8 points had greater disability, a lower cognitive function, and greater brain atrophy than those with an OSIT-J score of >8 points. Therefore, the cut-off point was thought to well reflect the disease burden of MS and the difference in pathological conditions between SPMS and RRMS patients. Furthermore, our results are consistent with those reported by a previous study in which the B-SIT was used to evaluate olfactory identification and discriminate SPMS from RRMS; this previous study showed that a B-SIT score ≤8 points indicated hyposmia and SPMS (15). This observation was also true in our study, despite the species and cultural backgrounds of the subjects differing between the two studies. The OSIT-J and B-SIT are similar tools for the evaluation of olfactory identification. Subjects are presented with 12 odorant items and asked to make a forced choice from multiple answers on the list. The consistency of the results of these two studies strongly supports the utility of olfactory identification for discriminating between SPMS and RRMS.

The results of our study favor the utility of olfactory identification as an indicator to monitor MS progression independent of racial and cultural background. However, there are some limitations. First, the usage rate of disease-modifying therapy differs among MS groups. In our study, SPMS patients used fingolimod more often, while RRMS patients used more dimethyl fumarate. However, differences in treatment patterns are thought to have had no impact on our results, since fingolimod, which is considered to have greater or equivalent efficacy to dimethyl fumarate, was used more often in SPMS patients, who had a greater impairment of the olfactory function and poorer clinical status. Second, since this study was a cross-sectional study, we did not evaluate the prognostic value of olfactory identification for secondary progression of MS in a longitudinal manner. The olfactory identification ability should be prospectively and frequently assessed in a sufficiently large cohort of RRMS patients to clarify its usefulness to predict the progression from RRMS to SPMS. In addition, we used the 3rd VW as a surrogate marker of central brain atrophy. A recent study demonstrated that the 3rd VW was a useful manual measure for brain volume in MS (28). However, since the 3rd VW reflects diffuse brain atrophy, including atrophy of the subcortical gray and deep white matter, our study did not identify the exact part of the brain that was affected. In particular, the olfactory cortex has been associated with olfactory identification (1). Detailed imaging studies may specifically demonstrate the impact of regional brain volume loss on olfactory identification; such imaging studies might prove that the olfactory identification test is an adequate tool for monitoring the progression of MS in daily clinical practice.

**Conclusion**

Olfactory dysfunction, which is a cardinal symptom of RRMS, was associated with the disease burden in MS and occurred more frequently and severely in patients with SPMS than in those with RRMS in our Japanese population. Olfactory dysfunction was also well-differentiated between these two diseases in association with cognitive impairment and brain atrophy. These results strongly suggest that olfactory dysfunction reflects neuropathological changes in MS as universal phenomenon. Thus, olfactory identification is a possible marker for disease progression in the clinical setting. Simple instruments for olfactory identification, such as OSIT-J, which do not require extensive time and labor to administer, were useful for evaluating the disease status of MS patients and may also provide clues to identify SPMS, for which there are no globally accepted diagnostic criteria at present, in daily clinical practice.

Informed consent was obtained from all participants.

The authors state that they have no Conflict of Interest (COI).

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