Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Abnormal pain perception in patients with Multiple System Atrophy

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ARTICLE INFO

Article history:
Received 24 April 2017
Received in revised form
26 October 2017
Accepted 3 December 2017

Keywords:
Multi system atrophy
Parkinson's disease
Pain processing
Pain thresholds
Pain tolerance

ABSTRACT

Introduction: Patients with Parkinson's disease or Multiple System Atrophy frequently experience painful sensations. The few studies investigating pain mechanisms in Multiple System Atrophy patients have reported contradictory results. In our study, we compared pain thresholds in Multiple System Atrophy and Parkinson's disease patients and healthy controls and evaluated the effect of L-DOPA on pain thresholds.

Methods: We assessed subjective and objective pain thresholds (using a thermotest and RIII reflex), and pain tolerance in OFF and ON conditions, clinical pain, motor and psychological evaluation.

Results: Pain was reported in 78.6% of Multiple System Atrophy patients and in 37.5% of Parkinson's disease patients. In the OFF condition, subjective and objective pain thresholds were significantly lower in Multiple System Atrophy patients than in healthy controls (43.8 °C ± 1.3 vs 45.7 °C ± 0.8; $p = 0.0005$ and 7.4 mA ± 3.8 vs 13.7 mA ± 2.8; $p = 0.002$, respectively). They were also significantly reduced in Multiple System Atrophy compared to Parkinson's disease patients. No significant difference was found in pain tolerance for the 3 groups and in the effect of L-DOPA on pain thresholds in Multiple System Atrophy and Parkinson's disease patients. In the ON condition, pain tolerance tended to be reduced in Multiple System Atrophy versus Parkinson's disease patients ($p = 0.05$).

Conclusion: Multiple System Atrophy patients had an increase in pain perception compared to Parkinson's disease patients and healthy controls. The L-DOPA effect was similar for pain thresholds in Multiple System Atrophy and Parkinson's disease patients, but tended to worsen pain tolerance in Multiple System Atrophy.

1. Introduction

Multiple system atrophy (MSA) is an orphan neurodegenerative disorder, characterized by the variable association of parkinsonism, autonomic failure, cerebellar and corticospinal symptoms [1]. Similar to patients with Parkinson's disease (PD) [2,3], MSA patients frequently experience painful sensations. Up to 70% of MSA patients report pain [4,5]. The types of pain in MSA have been described and categorized using selected and non-dedicated questionnaires [4,5]. Only two studies have investigated pain mechanisms in MSA patients, and they have reported contradictory results [6,7]. As observed in PD, abnormal pain processing may exist in MSA patients, contributing to the occurrence of pain.

In fact, central modification of pain processing resulting in abnormalities in pain perception in PD patients has been previously identified by our group and others [8–11]. These studies showed lowered subjective and objective pain thresholds compared to healthy volunteers, and abnormal hyperactivation in nociceptive brain areas, which were both reduced by L-DOPA administration [8–11].

Consequently, the aim of this study was to determine if pain symptoms in MSA could also be associated with a decrease in pain

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https://doi.org/10.1016/j.parkreldis.2017.12.001
1353-8020/

thresholds, and to characterize the L-DOPA effect on the patients' pain thresholds. The primary objective was to compare the pain threshold in MSA patients in the OFF condition versus healthy volunteers. Secondary objectives were to compare pain thresholds between MSA and PD patients in the OFF condition and the effect of L-DOPA on pain thresholds between these two groups. Finally, we investigated correlations between the pain threshold and motor status, depression and anxiety.

2. Patients and methods

2.1. Participants

In this prospective controlled study, MSA-P (MSA with predominant parkinsonian features) and PD patients diagnosed according to established criteria [12,13] were recruited consecutively from the Toulouse national MSA Reference Center (www.chu-toulouse.fr/-centre-de-reference-de-*l*-atrophie-multisystematisee) and from the Abnormal Movements Unit at the Expert Parkinson Center of the Toulouse University Hospital (www.chu-toulouse.fr). Healthy age- and gender-matched (+/− two years) controls (HC) with the two groups of patients were included from the Toulouse Clinical Investigation Center. The HC did not have any type of pain. For MSA and PD patients, the exclusion criteria were: cognitive impairment (MMS <26), treatment with neuroleptics, patients suffering from another pain condition (rheumatic disease, traumatic, orthopedic or peripheral nerve injury), patients with other than PD causes of parkinsonian syndrome and MSA-P. All patients had to stop their analgesic medication the day before the experiment.

2.2. Standard protocol approvals/registration and patients consents

The project was approved by the Research Ethics Committee and written informed consent was obtained from each subject. The sponsor was the Toulouse University Hospital. This trial is registered; No. NCT01577992.

2.3. Clinical assessment

2.3.1. All patients and controls were assessed with the support of the clinical investigation center pain thresholds

The subjective heat pain threshold was assessed using a Peltier-based contact temperature stimulation with a contact thermode (MSA Thermotest, Somedic AB, Sweden) [14] and measured on the thenar eminence of the most affected hemibody using the method of levels previously described in Dellapina et al., 2012 [15]. In MSA and PD patients, the subjective heat pain threshold was conducted in the OFF condition (withdrawal of 12 h of any dopaminergic treatments) and in the ON condition (1 h after administration of an oral dose of dispersible L-dopa, calculated to be equal to 150% of the morning dose of their current dopaminergic treatment, or 150 mg when MSA patients were not treated by L-DOPA). In HC, the subjective heat pain threshold was assessed without any treatment.

For the subjective threshold, we determined in both medication conditions an intensity-response curve while randomly applying a series of supraliminal stimuli. Each stimulus ran for 5 s (maximum intensity: 48 °C), with an interval of 60 s between each stimulation. After each stimulus, the patient had to rate the pain experienced using the Visual Analogue Scale (VAS: 0 = no pain, 10 = unbearable pain), which established a graph of the intensity of the response as a function of temperature. From the intensity-response curve, we determined the temperature corresponding to 75% of the maximum VAS. This temperature was applied twice at 5-min intervals to the patient. The pain tolerance threshold corresponded to the time until the stimulation became unbearable.

The nociceptive reflex RIII (objective pain threshold) was performed in the OFF and ON conditions and recorded using an Oxford synergy data acquisition electromyography device as previously described [10]. The RIII threshold was defined as the minimal intensity inducing an RIII reflex response (mean of the three measures).

The higher the subjective and objective heat pain thresholds are, the less patients are prone to feel pain. For all patients, the evaluation of pain thresholds and the filling of pain questionnaires were conducted according to the same sequence.

2.4. Clinical pain questionnaires

The clinical pain evaluation consisted of (i) the mean VAS over the last 7 days, (ii) the short form McGill Pain Questionnaire (SF-MPQ) consisting of 8 sensory and 9 affective items, (iii) the neuropathic pain symptom inventory (NPSI) (total score and 5 subscores: burning, squeezing, paroxysmal pain, provoked pain, paresthesia and dysesthesia), and (iv) the identification of different kinds of pain. First, the pain was related to parkinsonism if the patient reported at least three of the following five features: (1) the pain was chronologically related to parkinsonism (occurring at the onset of the parkinsonian syndrome); (2) the pain was located in the half of the body most severely affected; (3) the pain was influenced by dopaminergic drugs; (4) the pain was not related to any other evident etiology (rheumatic, traumatic or orthopedic disorders); (5) the patient identified a link between the pain and the disease [8,10,15]. Second, central neuropathic pain was considered if there was no radicular distribution and if the symptoms were defined as having the clinical characteristics of neuropathic pain defined with the DN4 interview questionnaire (burning, painful cold, electric shock, tingling, pins and needles, numbness, itching) [16,17]. Nociceptive pain can include dystonia-related pain, painful dyskinesia, pain symptoms arising from skeletal or articulation deformations, from parkinsonian rigidity or from postural abnormalities.

2.5. Other clinical assessments

In order to compare the L-DOPA effect on motor status between PD and MSA groups, we used the UPDRS III (Unified Parkinson's Disease Rating Scale) before and after L-DOPA challenge. The UMSARS (Unified Multiple System Atrophy Rating Scale) was only performed in the MSA group in the ON condition. Anxiety and depression were evaluated by the Hospital Anxiety and Depression Scale (HAD) in each group.

3. Statistical analysis

For descriptive analysis, quantitative parameters were expressed as mean ± standard deviation plus range and qualitative parameters as frequency and percentage.

Our goal was to have 80% power for detecting a threshold difference of 3° Celsius between MSA patients and controls with a two-sided test at the 5% significance level.

Assuming a standard deviation of 3.1° based on previous studies, 17 subjects were required in each of the two groups.

Demographic and clinical characteristics (quantitative variables) were compared between the three groups of subjects (MSA, PD and HC) using the Kruskal-Wallis rank-sum test, and the Wilcoxon rank-sum test was used for two by two comparison of groups.

In each group of patients, we compared pain thresholds, pain tolerance and the UPDRS III between the OFF and the ON conditions using a Wilcoxon sign-rank test.

Please cite this article in press as: F. Ory-Magne, et al., Abnormal pain perception in patients with Multiple System Atrophy, Parkinsonism and Related Disorders (2017), https://doi.org/10.1016/j.parkreldis.2017.12.001