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Assessment of cortico-spinal tract impairment in multiple system atrophy using transcranial magnetic stimulation

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Abstract

Objective: Among Parkinsonian syndromes, pyramidal signs suggesting cortico-spinal impairment are a hallmark of multiple system atrophy (MSA). Although it is crucial to diagnose correctly this disease to choose the appropriate treatment, the available diagnostic criteria lack sensitivity. Cortical excitability patterns assessed by transcranial magnetic stimulation (TMS) do not differentiate Parkinsonian disorders. TMS using triple stimulation technique (TST) accurately detects cortico-spinal impairment. We hypothesized that this technique could detect such impairment in MSA patients.

Methods: The TST was applied along with single and paired-pulse TMS to 31 patients fulfilling the diagnostic criteria for MSA-P ($n = 10$), MSA-C ($n = 4$), progressive supranuclear palsy (PSP; $n = 6$) and Idiopathic Parkinson's disease (IPD; $n = 11$) and 11 control subjects.

Results: Single and paired-pulse TMS patterns did not differ between any patient group. The TST pattern was abnormal in five MSA-P, one MSA-C and one PSP patients but not in IPD patients or controls. The mean TST ratio for MSA-P (86.6%) was significantly different from IPD (99.1%; $p < 0.05$) whereas ratios for MSA-C (92.1%) and PSP (93.3%) were not different from IPD or controls (99.5%).

Conclusions: These results suggest that TST is effective to assess cortico-spinal impairment in MSA.

Significance: TST might be useful for the diagnosis of atypical Parkinsonism.

Keywords: Transcranial magnetic stimulation; Motor evoked potentials; Triple stimulation technique; Multiple system atrophy; Parkinson's disease; Cortico-spinal tract

1. Introduction

Differentiating between idiopathic Parkinson's disease (IPD) and atypical Parkinsonian syndromes such as multiple system atrophy (MSA) can be rather tricky, especially in the early stages of the disease, despite the extensive use of the diagnostic criteria (Gilman et al., 1999; Osaki et al., 2002; Quinn, 1989). The more classical features of MSA such as autonomic dysfunction are frequently absent during the first few years of the disease (Osaki et al., 2002). In addition, MSA and IPD have a number of overlapping features such as asymmetry, resting tremor and levodopa responsiveness (Osaki et al., 2002). One of the clinical hallmarks of MSA is the presence of pyramidal signs suggesting cortico-spinal tract impairment (Quinn, 1989; Wenning et al., 2004; Wenning et al., 2003), as confirmed in anatomical post-mortem studies (Tsuchiya et al., 2000). However, these symptoms are as well seldom observed during the early stages of the disease (Osaki et al., 2002). Since the outcome and the therapeutic strategies differ between MSA and IPD, it is necessary to have reliable tools to differentiate between these diseases as early as possible.

During the past decade, several tools have been developed to address this issue. Magnetic resonance imaging (Schrag et al., 2000), as well as FDG PET (Eckert et al., 2005), dopamine transporter imaging (Scherfler et al., 2005) and cardiac MIBG-SPECT (Druschky et al., 2000), can help to differentiate between IPD and MSA. However,

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these techniques are not yet applicable to individual patients because of the interindividual variability involved. Electromyographic sphincter abnormalities seem to be both sensitive and specific means of diagnosing MSA, but this technique is rather invasive (Paviour et al., 2005).

Transcranial magnetic stimulation (TMS) of the brain is now used since two decades to study the integrity of motor pathways in a variety of diseases such as motor neuron diseases, multiple sclerosis and spinal cord injury (Curra et al., 2002; Di Lazzaro et al., 1999; Hallett, 2000). In patients with idiopathic Parkinson's disease (IPD), most TMS studies have shown the existence of normal central motor conduction time (CMCT) and normal motor evoked potential amplitudes (MEP), which are known to be indexes to cortico-spinal conduction (Cantello et al., 2002). In several previous studies, IPD patients have been reported to display normal resting motor threshold (RMT) (Cantello et al., 2002) and a reduced silent period duration (SP) that normalizes after L-Dopa treatment (Cantello et al., 2002; Manfredi et al., 1998; Priori et al., 1994). Authors of paired pulse studies on IPD patients have reported that intracortical inhibition (ICI) was significantly reduced in patients off treatment at rest (Cantello et al., 2002; Ridding et al., 1995), and showed partial recovery after levodopa intake (Strafella et al., 2000), while intracortical facilitation (ICF) seemed to remain unchanged (Cantello et al., 2002). However, discrepancies have been reported in several other studies (Berardelli et al., 1996; Kuhn et al., 2004).

Few TMS studies have been conducted so far on MSA patients. Two studies showed that the CMCT were higher in MSA than in IPD patients (Abbruzzese et al., 1997; Cruz Martinez et al., 1995). As far as the patterns of cortical excitability are concerned, Marchese et al. reported that patients with MSA of the Parkinsonian type (MSA-P) and vascular Parkinsonism showed a similar decrease in ICI, whereas patients with MSA of the cerebellar type had a normal ICI (Marchese et al., 2000). In a more recent study on various atypical Parkinsonian syndromes, a tendency towards a further decrease in ICI and an increase in the SP was observed in MSA in comparison with IPD patients (Kuhn et al., 2004). No such increase in the SP was encountered in another recent study (Wolters et al., 2004). Therefore, patterns of cortical excitability do not seem to differentiate between MSA and IPD.

TMS lacks sensitivity as a means of assessing cortico-spinal tract impairment. The triple stimulation technique (TST) detects cortico-spinal conduction failure more accurately and has been used for this purpose in a variety of neurological diseases (Attarian et al., 2005b; Humm et al., 2004; Magistris et al., 1998, 1999). In their large study of the TST, Magistris et al. had shown the existence of a cortico-spinal conduction failure in a small group including patients with a suspected diagnosis of MSA (Magistris et al., 1999). These preliminary results encouraged us to conduct a prospective study of both MSA and IPD patients.

The aim of this study, was to assess cortico-spinal tract impairment and cortical excitability patterns in patients with clinically defined MSA using several TMS techniques including the TST and to determine whether the latter provides a useful tool for the differential diagnosis of Parkinsonian syndromes.

2. Patients and methods

2.1. Subjects

This study was carried out on 14 patients with MSA, including 10 MSA patients of the Parkinsonian type (MSA-P), 6 with clinical features of progressive supranuclear palsy (PSP), 11 with IPD and 11 healthy age-matched control subjects. All these patients were recruited from the Department of Neurology at the Timone Hospital in Marseille, where they had been admitted for diagnostic purposes (MSA and PSP) or for pre-deep brain stimulation exploration (IPD).

All the MSA patients fulfilled the criteria for probable MSA (Gilman et al., 1999), all the PSP patients fulfilled the NINDS-SPSP criteria for probable PSP (Litvan et al., 1996), and the IPD patients were recruited among those due to undergo subthalamic stimulation, and had therefore been thoroughly explored. Dopa responsiveness was assessed in all patients but four by administering an acute dose of levodopa and subsequently assessing the motor effects using section III of the Unified Parkinson's Disease Rating Scale (UPDRS). Dopa responsiveness was assessed in the patients who were not given an acute dose of levodopa by comparing the UPRDS III scores before and after chronic levodopa treatment.

Clinical examination was performed by a movement disorder expert and motor symptoms were assessed using section III of the UPDRS in the OFF state, and the patients were classified depending on the severity of their Parkinsonian symptoms (mild = 0–20, moderate = 20–40, severe = 40–60, very severe >60). All neurophysiological recordings were carried out by the same investigator who was blinded to the diagnosis. Neurophysiological tests were performed on the clinically most affected upper limb or on the right limb when both sides were equally affected.

All patients were examined at least 12 h after antiparkinsonian drug withdrawal. All patients had an MRI-scan of brain. Patients were excluded if they showed abnormalities on their MRI-scans suggesting the occurrence of other pathological processes possibly interfering with the clinical pictures (severe white matter, vascular or space-occupying lesions).

Patients gave their informed written consent to the procedure in keeping with the Helsinki Declaration, and the study was also approved by the local Ethics Committee.

2.2. Magnetic motor cortex stimulation

TMS was performed as we previously described (Attarian et al., 2005a,b) on the hand-associated motor cortex