Cutaneous silent periods in multiple system atrophy

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Aim. The cutaneous silent period (CSP) is a spinal inhibitory reflex primarily mediated by A-delta fibers. Prolonged CSPs have been reported in patients with restless legs syndrome (RLS) and idiopathic Parkinson's disease (IPD). Dopaminergic medication normalizes the CSP, concurring with the effect of levodopa on CSPs. To date, CSPs have not been extensively studied in patients with multiple system atrophy (MSA). The purpose of this study was to confirm abnormal CSP findings in a group of MSA patients and to affirm the lack of influence of levodopa on CSPs during long-term treatment.

Methods. We investigated 15 patients (4 males, 11 females, age 58-71 years) who fulfilled the diagnostic criteria for possible MSA. Thirteen patients had predominant parkinsonian symptoms (MSA-P), 2 had predominant cerebellar signs (MSA-C). We recorded CSPs in thenar muscles following noxious digit II stimulation. Sixteen healthy volunteers (6 males, 10 females, range 24-56 years) served as control subjects for CSP recordings.

Results. Group average CSP onset was mildly delayed (P<0.01), whereas CSP end latency (P<0.001) were markedly delayed and CSP duration prolonged (P<0.001) in MSA patients compared to healthy controls. MSA patients on levodopa treatment did not differ in their CSPs from those without levodopa. The dose of levodopa did not correlate to any CSP parameter.

Conclusion. The observed CSP prolongation corroborates previous findings in a limited number of MSA patients. The ineffectiveness of long-term levodopa on CSP abnormalities is consistent with its poor clinical effect in MSA.

Key words: multiple system atrophy, atypical parkinsonism, spinal reflex, cutaneous silent period, levodopa

INTRODUCTION

Multiple system atrophy (MSA) is a sporadic and progressive neurodegenerative disorder characterized by autonomic failure in combination with parkinsonism or cerebellar ataxia. Apart from clinical diagnostic criteria neuroimaging studies may help in the differential diagnosis, as well as autonomic and neurophysiological testing early on.

Cutaneous nerve electrical stimulation produces transient suppression of electromyographic (EMG) activity in a voluntarily contracted muscle in the same extremity, known as the cutaneous silent period (CSP) (ref.12,13). The afferent nerve fibers mediating the CSP are slowly-conducting A-delta fibers. The exact neural mechanism of inhibition has yet to be elucidated; the CSP could be evoked either by postsynaptic inhibition of the motoneuron itself or through presynaptic inhibition of excitatory inputs to those motoneurons which sustain the voluntary contraction. Several characteristics of the CSP depend on physiological parameters, e.g. the combination of nerve stimulated and muscle recorded from.

Altered CSPs have been demonstrated in movement disorders such as dystonia, idiopathic Parkinson’s disease (IPD), and restless legs syndrome (RLS) (ref.16-19). Dopaminergic medication can normalize the abnormalities in IPD (ref.18) and RLS (ref.19). Four patients with MSA were reported with prolonged CSPs after a single levodopa challenge of 200 - 400 mg (ref.18). These findings, however, have so far not been confirmed in a larger group of patients. We therefore investigated CSPs in a group of MSA patients who were on long-term levodopa treatment and compared findings with a group of MSA patients in whom levodopa had been terminated.

MATERIALS AND METHODS

We investigated 15 patients (4 males, 11 females, age 58-71 years) who fulfilled diagnostic criteria for possible MSA (ref.1) – a sporadic, progressive neurodegenerative disorder with onset after age 30 years, characterized by parkinsonism or a cerebellar syndrome, and at least one feature suggesting autonomic dysfunction (otherwise unexplained urinary urgency, frequency, or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic hypotension). Diagnosis was established in the
Movement Disorders Center, Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine and General University Hospital in Prague. No patient had a history or clinical evidence of a psychiatric disorder. Computed tomography or magnetic resonance imaging excluded tumors, lacunar infarcts, hydrocephalus, and subcortical ischemic encephalopathy. Sixteen healthy volunteers (6 males, 10 females, age 24 – 56 years) without evident history of neurological or psychiatric disorders and no recent intake of any medication served as control subjects. All participants granted informed consent. The study was approved by the local Ethics committee of Na Homolce Hospital, Prague, in compliance with the latest Declaration of Helsinki.

Neurophysiological investigation was performed with standard electrodiagnostic equipment (Dantec Keypoint, Dantec-Medtronic, Skovlunde, Denmark). Subjects lay supine with arms relaxed and hands held in a slightly pronated position with the fingers extended. CSPs were obtained bilaterally in all patients and in most control subjects, sequentially in right and left thenar muscles. Electrical square pulses (0.5 ms duration, 0.5 – 0.7 Hz stimulation rate, 20 times the sensory threshold intensity) were delivered with ring electrodes located at the intermediate and distal phalanges of the index finger. Sensory thresholds were established in each subject as previously described. Stimuli were applied during isometric thumb abduction against a velcro strap on command for five seconds with self-estimated half-maximum strength. Visual and auditory feedback of the EMG signal was provided in order to facilitate control of muscle activity. Muscle force, however, has recently been shown to be less critical for CSP recordings than previously thought. EMG activity was obtained with surface electrodes placed over abductor pollicis brevis muscle belly and tendon. Five single sweeps of 500 ms were recorded with filters set at 20 and 5000 Hz. A CSP was defined as clear reduction or absence of voluntary EMG activity following the stimulus at appropriate latencies. Mean values of five responses were calculated off-line for each patient. Unfortunately,

<table>
<thead>
<tr>
<th>Number</th>
<th>Age [years]</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration of disease [months]</th>
<th>L-dopa [mg/d]</th>
<th>Reflexes</th>
<th>Pyramidal signs</th>
<th>Co-morbidities</th>
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<tr>
<td>1</td>
<td>66</td>
<td>F</td>
<td>MSA-P</td>
<td>21</td>
<td>0</td>
<td>Hyporeflexia</td>
<td>L2-S2</td>
<td>None</td>
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<tr>
<td>2</td>
<td>71</td>
<td>M</td>
<td>MSA-P</td>
<td>66</td>
<td>0</td>
<td>Normal</td>
<td>None</td>
<td>Diabetes mellitus type II, on diet</td>
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<td>3</td>
<td>58</td>
<td>M</td>
<td>MSA-P</td>
<td>34</td>
<td>600</td>
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<td>L5-S2</td>
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</tr>
<tr>
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<td>F</td>
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<td>16</td>
<td>1000</td>
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<td>None</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>F</td>
<td>MSA-P</td>
<td>51</td>
<td>350</td>
<td>Areflexia</td>
<td>L5-S2</td>
<td>Babinski bilateral, Cervical spondylotic stenosis at C5-C7 level</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>F</td>
<td>MSA-P</td>
<td>49</td>
<td>1500</td>
<td>Normal</td>
<td>L2-S2</td>
<td>Hyperreflexia C5-C8</td>
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<tr>
<td>7</td>
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<td>825</td>
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<td>None</td>
</tr>
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<td>0</td>
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<td>L2-S2</td>
<td>Babinski right</td>
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<tr>
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<td>750</td>
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<td>None</td>
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<td>L5-S2</td>
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<td>1450</td>
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<td>MSA-P</td>
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<td>C5-8</td>
<td>Hyperreflexia L2-L4</td>
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<td>Areflexia</td>
<td>L5-S2</td>
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<td>F</td>
<td>MSA-P</td>
<td>49</td>
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<td>Normal</td>
<td>None</td>
<td>Diabetes mellitus type II, on insulin, lumbar spondylotic stenosis at L3-L5 level</td>
</tr>
<tr>
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<td>MSA-C</td>
<td>76</td>
<td>125</td>
<td>Normal</td>
<td>Babinski bilateral</td>
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the equipment did not allow for rectification of the raw EMG signal, so that appropriate “on-line” averaging of the EMG traces without phase cancellation was not possible. Statistical analysis was performed with SPSS 20.0 (IBM SPSS Inc., Chicago, IL, USA). Mean ± standard error was calculated from all mean values obtained in each subject and compared with Mann-Whitney-U test between groups. Spearman correlation was calculated for each parameter (onset and end latency, as well as duration of CSPs) in order to identify any significant changes relative to levodopa dose. A P-value of <0.025 was considered significant.

RESULTS

All patients and healthy controls were able to complete the study. Patient demographics are shown in Table 1. Most patients presented with sphincter dysfunction and orthostatic problems. Cerebral MRI findings included middle cerebellar peduncle atrophy and/or lamellar atrophy of the cerebellum, as well as pontine and putaminal atrophy (Table 2). Thirteen patients had predominant parkinsonian symptoms (MSA-P), two had predominant cerebellar signs (MSA-C), consistent with a known preponderance for MSA-P in Europe23. One patient with cervical myelopathy had an absent CSP on the right side, which is not unusual even in mild cervical spondylotic myelopathy24. Nine patients were on levodopa treatment with an average of 897 mg/d. No patient received dopamine agonists. Signs of upper motoneurone lesion (Babinski sign, hyperreflexia) were noted in five patients (9 limbs); signs of lower motoneurone lesion (hyporeflexia, areflexia) were noted in seven patients (14 limbs) (ref.11). No patient had a history or clinical evidence of radiculopathy. One patient also had insulin-dependent diabetes mellitus.

CSP onset and end latencies were significantly delayed and CSP duration was significantly prolonged in patients as compared to healthy control subjects (Table 3). There was no difference in CSP parameters between patients taking levodopa (n=9) and those who were not (n=6): CSP onset latency: 83.5 ± 2.7 ms versus 86.4 ± 4.0 ms; CSP duration: 69.9 ± 4.7 ms versus 68.9 ± 4.3 ms; CSP end latency: 157.4 ± 5.1 ms versus 155.3 ± 4.4 ms (P>0.5 each). Furthermore, there was no correlation of levodopa medication to any of the CSP parameters (onset: ρ = -0.348;...
duration: $\rho = 0.121$; end: $\rho = -0.70$; $P>0.06$ each), despite similar disease duration (mean ± standard deviation) in patients with and without levodopa (47.9 ± 19.7 versus 51.3 ± 22.4 months, $P>0.5$). Findings in the two patients with MSA-C were not consistently different from those in patients with MSA-P. No formal statistical comparison, however, was performed between MSA-C and MSA-P due to the inhomogeneous distribution. Representative examples are shown in Fig. 1.

**DISCUSSION**

MSA is a rare progressive neurodegenerative disorder presenting with extrapyramidal, cerebellar, pyramidal and autonomic signs. Early recognition of this disease has important implications for a patient’s medical treatment and clinical management. Magnetic resonance imaging and diffusion tensor imaging are the key diagnostic methods to differentiate MSA from IPD (ref.2-4), however, simple neurophysiological testing could aid in the early differential diagnostic process7,11.

This study describes delayed CSP onset and prolonged CSP duration in 15 patients with MSA, thus confirming previously reported findings in a smaller sample of four MSA patients. Furthermore, long-term levodopa exerted no significant influence on any CSP parameter, concurring with its poor clinical efficacy in this disorder. We refrained from performing an additional levodopa challenge, as this had already been done in those patients without levodopa treatment without clinical effect, and it has been described in the literature: Serrao et al.18 reported an acute levodopa challenge of 200 to 400 mg without effects on UPDRS scores or on CSP duration in their four patients with MSA. In the present study, patients receiving long-term levodopa up to 1500 mg daily did not differ significantly in any CSP parameter from patients without levodopa.

To date, reports on dopaminergic influence on cutaneomuscular reflexes have been controversial: opposite effects were reported in RLS (ref.19,25), as well as in IPD (ref.18,26,27). Part of this discrepancy favors distinct spinal inhibitory circuitry mediated by low- and high-threshold afferents13,18,26-30, with the possibility that dopaminergic influence is exerted only on low-threshold afferent circuitry. The latter may contribute to the electrically evoked CSP (ref.28) due to concomitant activation of low-threshold afferents which inevitably occurs when applying electrical stimuli to peripheral nerves.

On the other hand, CSPs evoked by the same type of electrical stimulation to the index finger were similarly prolonged in IPD and MSA, while only in IPD patients levodopa shortened the CSPs to normal durations. This strongly implies an effect of basal ganglia on spinal excitability which is deficient in MSA, a disorder characterized by poor or entirely absent effect of dopaminergic medication31. Basal ganglia exert well-known modulatory influences on brainstem circuitry such as the blink reflex23,32 and the auditory startle reaction. MSA patients in particular are characterized by exaggerated auditory startle reactions6, a finding also seen to a lesser extent in patients with RLS (ref.33). Thus, the basal ganglia likely influence spinal excitability at least in part via reticulospinal pathways. Reticulospinal neurons are also known to be involved in flexor withdrawal reflexes, which are also disinhibited in RLS (ref.44). Flexor withdrawal reflexes likely share common spinal circuitry with CSPs. In fact, both are evoked by A-delta fibers, they have a similar distribution among various limb muscles in upper and lower extremities, and both are involved in protective movement behavior22,35. Thus the reticulospinal system may in fact be a common link interposed between basal ganglia and spinal cord with respect to dopaminergic influence on spinal inhibitory circuitry which causes increased excitability or reduced inhibition, thus leading to shortened CSP duration.

Delayed onset of the CSP has previously been attributed to dysfunction of corticospinal neurons based on findings in stroke, amyotrophic lateral sclerosis and cervical compressive myelopathy24,36. Arguably it seems difficult to envision how a motor pathway that is inhibited by A-delta afferent input can facilitate the same circuitry in a way that the onset of its own inhibition is preponed. But up to this point no better explanation has been offered.

An alternative contribution to a delay in CSP onset could derive from large-diameter efferent fiber polyneuropathy, an often underrecognized feature of MSA (ref.13). Alpha-

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**Fig. 1.** Representative examples of cutaneous silent periods in a normal subject (upper panel) and a patient with multiple system atrophy (lower panel).
motoneurones convey input from the spinal cord to the muscles; thus when they conduct more slowly, their inhibition would also become apparent later. Finally, our normal subjects were younger, which may also explain some minor effect on the results, as a mild effect of age on CSP duration has been reported\(^3\). The findings reported here, however, clearly exceed possible age-associated effects. To date, little is known about neurotransmitters involved in CSP generation. Previous studies indicated no influence of benzodiazepines (diazepam) (ref.\(^{39}\)), opiates (fentanyl) (ref.\(^{39}\)), antihistaminics ( cetirizine) (ref.\(^{40}\)), or GABA\(_b\) agonists (baclofen) (ref.\(^{38,41,42}\)). Recently, increased CSP duration following tramadol application has been attributed to its monoaminergic action leading to inhibition of serotonin and noradrenaline reuptake\(^{38}\).

In summary, patients with MSA present with delayed and prolonged CSPs in comparison to healthy control subjects. These CSP abnormalities are not normalized, unlike in patients with IPD, by acute or chronic levodopa administration, and this concurs with the poor clinical response to levodopa in MSA. It remains to be tested whether the ineffectiveness of levodopa on CSP alteration can have clinical value in the differential diagnosis of MSA.

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