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Subclinical autonomic disturbances in multiple sclerosis

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Abstract We compared results from non-invasive autonomic testing [sympathetic skin responses (SSR), heart beat variation during deep breathing, and orthostatic manoeuvre with transcranial Doppler monitoring in 22 patients] with motor and somatosensory evoked potentials (MEP and SEP) in 30 unselected patients with multiple sclerosis. We found a similarly high yield of pathological results for SSR, MEP and SEP (66.7%, 65.5%, and 69%, respectively). When analysed for each limb ($n = 120$), SSR were highly correlated with MEP and SEP (for both $P < 0.001$). Heart beat variation was reduced in only 3 patients. In 4 of 22 patients orthostatic manoeuvre induced a pathological decrease in cerebral blood flow velocity despite normal systemic blood pressure being maintained. We conclude that SSR may be a useful additional diagnostic tool in patients with multiple sclerosis. Cerebral dysautoregulation is a rather frequent finding, although its significance is not known.

Key words Multiple sclerosis · Dysautonomia · Sympathetic skin responses · Cerebrovascular autoregulation

Introduction

Multiple sclerosis (MS) is a demyelination disorder of the central nervous system affecting motor, sensory and autonomic pathways. Autonomic involvement often presents with bladder disturbances and disorders of thermoregulatory sweating, the latter usually not reported by the patient [13]. Less frequently, orthostatic hypotension with some abnormalities on cardiovascular testing is reported and occasionally asymtomatic diminished heart beat variation may occur during deep breathing [3, 12, 14]. The latter may reflect reduced parasympathetic outflow, which is supported by detection of up-regulated acetylcholine receptors in those patients with progressive MS [1]. Cardiac arrhythmias [16] and neurogenic pulmonary oedema (rarely reported) [6] are probably due to brain stem lesions. Abnormalities of the sympathetic nervous system have been suggested as responsible for compromised immunological function, as in active progressive MS denervation hypersensitivity and up-regulated β-adrenergic receptors of immune cells have been demonstrated [8]. In this study sympathetic skin response (SSR) was often abolished and this fact was interpreted as general sympathetic dysfunction. In another study [19], however, asymmetrical responses were also found, which are more likely to be due to focal lesions of the central autonomic pathways. These authors compared SSR with somatosensory evoked potentials (SEP) and visual evoked potentials (VEP) and found a similar yield of pathological results for all methods in their severely affected patients. They suggested that SSR could be a suitable additional diagnostic method in patients with MS. However, interpretation of pathological SSR is difficult as the pathways of central sympathetic fibres mediating emotional sweating are poorly defined. They may arise in the cerebral hemispheres and travel down ipsilaterally to the lower brain stem as shown by SSR studies in monofocal brain lesions [10]. Spinal sympathetic pathways, known as the tractus intermediolateralis, probably cross at the thoracic level [17]. The aim of our study was to investigate autonomic pathways in unselected patients with MS by means of SSR, heart beat variation during deep breath-

ing, and systemic blood pressure/transcranial Doppler (TCD) monitoring during orthostatic manoeuvre and to compare them with clinical and neurophysiological data.

Methods

Patients and methods

Thirty patients with multiple sclerosis (definite form $n = 26$, probable form with typical CSF findings $n = 4$, according to the criteria of Poser et al. [15]) were studied prospectively with bipalmar and biplantar SSR, heart beat variation during deep breathing, and systemic blood pressure/cerebral blood flow monitoring during orthostatic manoeuvre. The latter was performed in only 22 patients who had a bone window for TCD and could perform active standing. In addition, magnetic motor evoked potentials (MEP) and SEP were performed. The findings were compared with course, duration, signs and symptoms of the disease. Severity of the disease was graded by using Kurtzke's expanded disability status scale (EDSS) [9]. Patients with known peripheral nerve abnormalities were excluded from the study.

SEP were recorded by a Nicolet pathfinder EP system; MEP and SSR were obtained by Medelec TECA mystro or sapphire EMG machines. Magnetic MEP were studied with a Magstim 200 (nonfocal coil, 8.5 cm diameter, maximal magnetic field 2 T) performing transcranial (with slightly pre-innervated muscles) and cervical stimulation (with relaxed muscles). Stimulation was done with 1.5 × threshold and three reproducible responses were obtained. Conventional surface electrodes recorded compound muscle action potentials (CMAPs) of the first dorsal interosseous (IDI) and tibialis anterior muscle (TA). Correlation between central motor conduction time (CMCT) and age ($r = 0.18$) tended to be higher than between CMCT and height ($r = 0.1$), but was not statistically significant in both instances. However, as the patients' mean age was very low, normal MEP values were divided into three age subgroups for better comparability. Upper limits (mean + 2 SD) for CMCT were 9.6 ms (IDI) and 18.1 ms (TA) (20- to 30-year-old controls, $n = 20$), 10.8 ms (IDI) and 17.3 ms (TA) (31- to 60-year-old controls, $n = 20$), and 10.4 ms (IDI) and 18.7 ms (TA) in controls older than 60 years ($n = 20$). Right-left difference was 1.9 ms (mean + 2 SD) for all recordings. In addition, amplitudes of MEP were thought to be pathological if the side-to-side differences were greater than 50% and transcranial/peripheral ratios < 15% (ulnar/peroneal nerve stimulation at wrist and capitulum fibulae), as such ratios were never observed in our controls. Patients with a pathological peripheral motor conduction were excluded from the study. SEP were recorded at C3′ an C4′ and at Cz′ after median and tibial nerve stimulation, respectively, with the reference at Fz. Normal values were obtained in 50 controls. Upper limits (mean + 2 SD) for N 20 were 22 ms (absolute value) and 1.9 ms (side-to-side difference). The corresponding values for P 40 were 43.9 ms and 2 ms, respectively. Correlation between N20/P40 values and both age and height was very low ($r < 0.1$) and was in neither case statistically significant. With the patients supine, SSR were recorded simultaneously from both palms and feet with the active electrode in a palmar and plantar position, and the inactive electrode at the dorsum of the hand and foot, respectively. Room temperature was 22–24° C and skin temperature was above 30° at the recording sites. Five random electrical stimuli (with intervals of at least 30 s) were delivered to both supraorbital nerves (40 mA, 0.1 ms duration). The values of each trial [latency: absolute value and right-left difference; amplitude (peak-to-peak): absolute value and side-to-side ratio] were recorded and mean values were calculated. Filter setting was 1 Hz to 2 kHz. Upper limits for palmar and plantar latencies obtained in 30 controls were 1.91 and 2.62 s (mean + 2 SD), respectively. Right-left difference for latency was 0.1 s and right-left ratio for amplitude was 41.4% (for both, mean + 3 SD). Amplitudes were also considered pathological when they were below range (palmar < 0.4 mV, and plantar < 0.2 mV). Results of SSR and evoked potentials were compared with the values obtained in normal controls and considered to be "normal" or "pathological" for each limb.

Heart beat variation was recorded in relaxed patients in a supine position. RR interval was measured with a standard EMG single fibre program and beats per minute were calculated. Breathing rate was 6/min. Lower limits (mean 2 SD) of normal controls ($n = 60$) were age dependent (18–30 years > 15 beats, 31–50 years > 11 beats/min 51–65 years > 9 beats/min and > 65 years > 5 beats/min).

Arterial blood pressure was measured with the subject in a supine position and 30 s after active standing. Mean cerebral blood flow velocity of the left middle cerebral artery (MCA) was continuously monitored by TCD with the subject lying and standing. According to the criteria of our laboratory, systemic blood pressure dysregulation was established if systolic blood pressure fell more than 20 mmHg after standing up. Cerebrovascular dysregulation was diagnosed when the mean blood flow velocity in the MCA decreased more than 20% below the supine value [4].

For statistical analysis, Student's t-test and chi square test were used. Regression analysis was performed with SAS software modules.

Results

The 30 patients (7 men, 23 women) had a mean age of 36 years (SD 11 years, range 17–57). The patients were free of centrally acting drugs, in particular anticholinergics and sympatholytics. Clinical presentation consisted of nystagmus, paroxysmal dystonia, facial palsy, limb ataxia (each $n = 1$), double vision ($n = 2$), optic neuritis ($n = 3$), sensory disturbances ($n = 3$), hemiparesis ($n = 6$), paraparesis ($n = 6$) and quadriparesis ($n = 6$). Four patients had laboratory-supported probable MS. The other 26 patients had definite MS, with typical cerebrospinal fluid abnormalities at the time of examination in 23 of them. Mean duration of the disease was 8 years (SD 8 years) with a range of 4 weeks of 37 years. The EDSS yielded a mean score of 4.1 (SD 1.6, range 1.5–8.5).

Sweating disorders, e.g. asymmetrical sweating or a decrease below a distinct level, were not evident in our patients. However, we did not perform qualitative or quantitative evaporative studies in our patients.

Vasomotor abnormalities were also not evident in our patients. Skin temperatures measured over the SSR recording sites were not asymmetrical even in patients with asymmetrical electrophysiological findings, making severe vasomotor abnormalities unlikely. However, this issue may only be appropriately studied by examination of skin blood flow.

Orthostatic problems were reported by 4 patients. During orthostatic manoeuvre, which was performed in 22 patients, only 2 of them showed a pathological decrease in systemic blood pressure with normal autoregulation in 1 (Fig. 1) and dysautoregulation in the other. In one asymptomatic patient a pathological systemic blood pressure decrease was found. Another 4 patients showed a significant decrease in cerebral blood flow velocity in the MCA de-

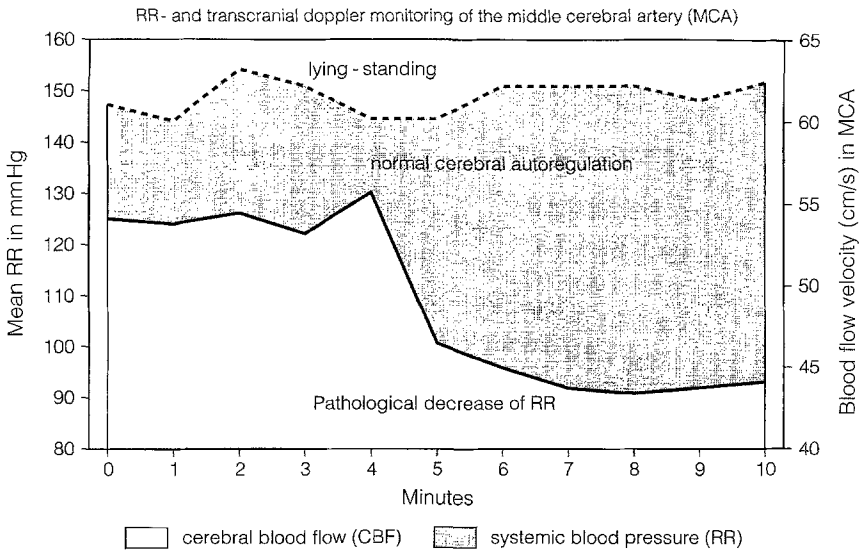

Fig. 1 Simultaneous monitoring of systemic blood pressure *(lower)* and cerebral blood flow *(CBF)* velocity *(upper)*. Note the pathological decrease in systemic blood pressure in the standing position with normal cerebral autoregulation

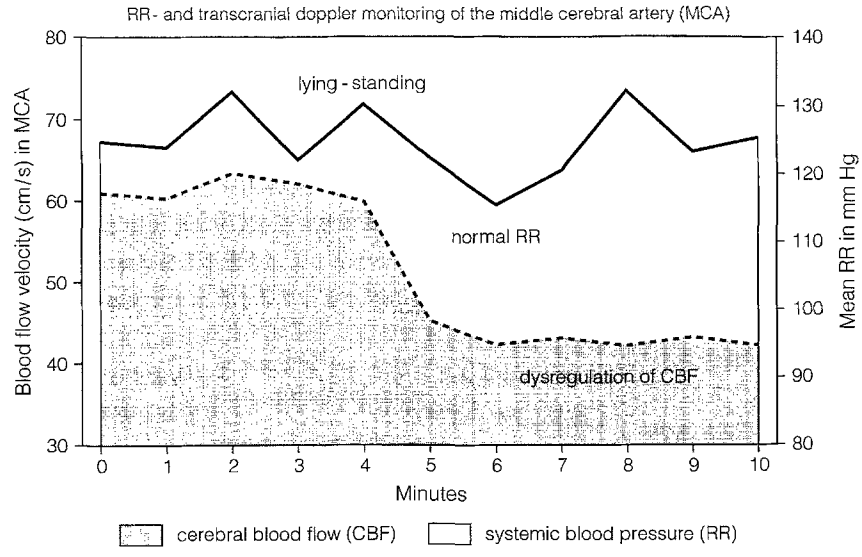

Fig. 2 In this patient without orthostatic problems a pathological decrease in cerebral blood flow velocity occurs in spite of maintained normal systemic blood pressure during change of position

spite maintenance of normal systemic blood pressure (Fig. 2), again without symptoms. A slightly pathological heart beat variation during deep breathing was found in only 3 patients. Disorders of micturition were present in 12 patients. Clinical presentation of these patients was facial palsy in 1, hemiparesis in another 2, and paraparesis or quadriparesis in all remaining patients. Two patients with quadriparesis had also fecal incontinence and severe impotence. Urodynamic studies were performed in only 3 patients, revealing sphincter/detrusor dyssynergia in 2 cases and detrusor hyperreflexia in another.

Neurophysiological studies yielded pathological results for SEP in 20 of 29 patients (69%), for MEP in 19 of 29 patients (65.5%), and for SSR in 20 of 30 patients (66.7%). The site of pathological SSR in 3 of 6 patients with hemiparesis was consistent with the clinical presentation as well as the pathological MEP and SEP. An abnormal SSR was found in all but 1 patient with paraparesis and quadriparesis (11 out of 12), indicating severe spinal involvement. Half of the remaining patients (9 out of 18) showed pathological SSR findings. The results of SSR are summarized in Table 1. An increased SSR latency was a rather infrequent finding, whereas decreased amplitudes, absent responses and pathological right-left differences were common (Fig. 3). When all limbs were

Table 1 Sympathetic skin responses (SSR) in 120 limbs

Absent response		11 (9.2%)
Increased latency	– absolute value	2 (1.7%)
	– right vs left	9 (7.5%)
Decreased amplitude	– absolute value	36 (30%)
	– right vs left	10 (8.3%)

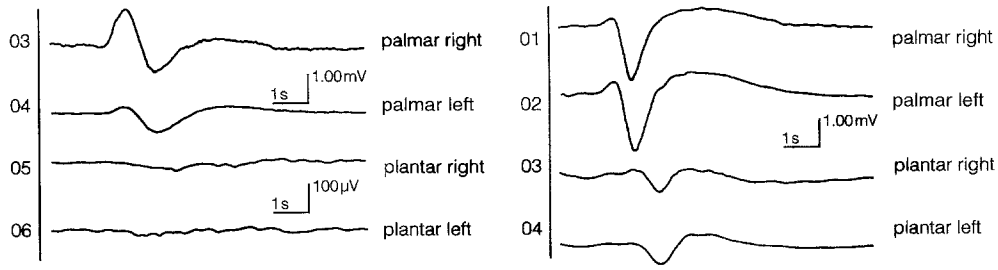

Fig. 3 Sympathetic skin responses in a control *(right)* and in a patient with multiple sclerosis *(left)*, showing decreased left palmar and absent plantar responses

Table 2 Duration, mean score and neurophysiological findings (*MEP* motor evoked potentials, *SEP* somatosensory evoked potentials, *n.s.* not significant

[a] SEP and MEP were performed in 29 patients

Duration	Score mean (SD)	Abnormal MEP[a]	Abnormal SEP[a]	Abnormal SSR
– 5 years ($n = 14$)	3.18 (0.94)	5/13	8/14	7/14
> 5 years ($n = 16$)	4.88 (2.87)	14/16	12/15	13/16
	$P < 0.05$	$P < 0.01$	$P > 0.05$, n.s.	$P > 0.05$, ns

Table 3 Score, duration and neurophysiological findings

[a] SEP and MEP were performed in 29 patients

Score	Duration: mean (SD)	Abnormal MEP[a]	Abnormal SEP[a]	Abnormal SSR
< 4 ($n = 15$)	4.2 (4.8)	7/15	9/15	9/15
4–8.5 ($n = 15$)	12.0 (8.4)	12/14	11/14	11/15
	$P < 0.01$	$P < 0.05$	$P > 0.05$, n.s.	$P > 0.05$, n.s.

Table 4 Course of disease and associated findings

[a] SEP and MEP were performed in 29 patients

Course	Duration Mean (SD)	Score Mean (SD)	Abnormal MEP[a]	Abnormal SEP[a]	Abnormal SSR
Remitting-relapsing ($n = 14$)	2.3 (2.7)	3.1 (0.8)	4/15	6/14	6/14
Progressive ($n = 16$)	13.1 (7.5)	5.0 (1.5)	15/15	14/15	14/16
	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.01$	$P < 0.05$

compared, a significant correlation was found for SSR and MEP ($P < 0.001$), and SSR and SEP ($P < 0.001$). In cases with normal SEP and SSR, MEP were also normal. In 1 patient with both normal MEP and SSR pathological SEP were found. In another 2 patients with both normal MEP and SEP, results of SSR were abnormal. Patients with normal results for SSR, MEP and SEP showed no statistically different amplitude or latency of SSR when compared with controls ($P > 0.05$). Comparison of SSR with results of orthostatic manoeuvre did not show a significant correlation ($P > 0.05$). However, disorders of micturition were correlated with MEP of TA muscle, tibial nerve-SEP and plantar SSR (all $P < 0.05$). When comparing course and duration of the disease and EDSS scores with findings of SEP, MEP and SSR, the strongest correlation was found between neurophysiological findings and the course of the disease. When neurophysiological data were compared with groups of low or high scores as well as long and short duration only MEP showed some significant correlation. The complete data are shown in Tables 2–4.

Discussion

In our study there was a high yield of pathological SSR findings in a group of unselected MS patients. Yokota et al. [19] investigated SSR in severely affected patients and found a similar high sensitivity when compared with VEP and SEP. They, therefore, suggested that SSR is suitable for neurophysiological work-up in MS patients. In our experience some features of normal SSR have to be considered in order to increase the sensitivity of SSR as a diagnostic tool. Although SSR vary considerably in latency and amplitude from trial to trial, they show very low side-to-side differences in latency and nearly stable right-left ratios of amplitude and should therefore be taken into account. This is of significance when focal abnormalities rather than a general dysfunction (e.g. autonomic neuropathy) of the sympathetic nervous system have to be detected.

In our study SSR were highly correlated with MEP and SEP when analysed for each limb. This is in accordance with our results for SSR in monofocal brain lesions, suggesting a close topographical relationship of sensory, motor and sudomotor fibres mediating emotional sweating [10]. The frequent finding of asymmetrical SSR in both

remitting-relapsing and progressive MS favours focal lesions of autonomic fibres, i.e. hemispheric subcortical or brain stem or spinal lesions, rather than a general sympathetic dysfunction. In a recent study [18] distinct abnormalities of diverse cardiovascular autonomic tests were found, actually not attributable to impairment of vagal or sympathetic mediated reflexes. Multiple, e.g. brain stem or subcortical lesions, were thought to be responsible for the unusual findings. Accordingly, in our study only 2 patients showed an orthostatic dysregulation which might be due to a diminished baroreceptor-mediated pressor response. However, in 4 patients a pathological autoregulation of cerebral blood flow during orthostatic manoeuvre occurred despite systemic blood pressure remaining constant. Based on our 5-year experience with simultaneous blood pressure/cerebral blood flow monitoring we believe bilateral pathological autoregulation in spite of normal systemic blood pressure to be a very rare finding. We have observed this pattern only in a few cases of subcortical arteriosclerotic encephalopathy. This finding is especially surprising because most patients, as in this study, lack orthostatic symptoms. However, the significance of this finding is not known, as the mechanisms involved in cerebral autoregulation are still under discussion. Besides established metabolic influences myogenic as well as neural factors have been proposed. Some experimental data have suggested both central noradrenergic [2, 7] as well as postganglionic sympathetic pathways [5] to be involved, but this remains speculative. Moreover, anticholinergic vasodilator pathways of the trigeminovascular system may also be of relevance [11].

Although in this study results of SSR, MEP and SEP were significantly correlated with the disability score and the duration of the disease, the strongest correlation was found for the criterion "course of the disease" by dividing into remitting-relapsing and progressive forms. This feature may indicate more accurately the underlying extent and severity of demyelination. This is in accordance with the known fact that the course of the disease is of high prognostic importance.

In this study, we did not analyse the correlation of MRI findings with the kind of autonomic disturbances, because of the multifocal nature of the disease. In our opinion, monofocal diseases of the central nervous system should first be studied in order to correlate autonomic disturbances with topographical aspects.

In summary, SSR can be recommended for neurophysiological work-up in MS because this method is easy to perform and may provide additional information regarding subclinical lesions of the central autonomic pathways.

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