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MOVEMENT DISORDERS - SHORT COMMUNICATION

The cold hand sign in multiple system atrophy: skin perfusion revisited

K. Pietzarka · M. Reimann · C. Schmidt · B. Herting · L. Schöls · H. Reichmann · D. Berg · Christoph Schrader · Tjalf Ziemssen

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Abstract The cold hand sign (CHS) is a distinct feature of multiple system atrophy (MSA), but its pathophysiology is poorly understood. We, therefore, conducted a study to examine the skin temperature and the skin blood flow at rest and after local heating in 6 age-matched MSA patients with CHS (MSA + CHS), 18 MSA patients without CHS (MSA – CHS) and 13 patients with idiopathic Parkinson's disease (PD). Basal skin temperature and blood flow were significantly lower in MSA + CHS patients than in MSA – CHS or PD patients. Local heating induced a greater response in terms of amplitude in MSA + CHS compared to MSA – CHS and PD. Considering kinetics, skin blood flow increment per 1°C was higher in MSA + CHS than MSA – CHS but was similar when compared to PD patients. Skin blood flow rate (change per second) did not differ among the groups. Our findings suggest that despite impaired basal skin perfusion, the skin vasomotor response to local heating is intact in MSA + CHS but disturbed in MSA – CHS. By measuring skin temperature and blood flow, the presence of CHS can be diagnosed in MSA patients. Further studies are necessary to understand regulation of skin perfusion in patients with extrapyramidal disease.

Keywords Autonomic nervous system · Multiple system atrophy · Autonomic dysfunction · Cold hand sign · Skin perfusion · Parkinson's disease

K. Pietzarka · M. Reimann · C. Schmidt · T. Ziemssen (✉)
Autonomic and Neuroendocrinological Laboratory,
Department of Neurology, University of Technology Dresden,
Fetscherstraße 74, 01307 Dresden, Germany
e-mail: tjalf.ziemssen@uniklinikum-dresden.de
URL: http://www.neuro.med.tu-dresden.de/anf

M. Reimann · T. Ziemssen
Research Group Neuro-Metabolism, Department of Neurology and Medicine III, University of Technology Dresden, Dresden, Germany

B. Herting · H. Reichmann
Parkinson Research Group, Department of Neurology, University of Technology Dresden, Dresden, Germany

L. Schöls · D. Berg
Department of Neurodegenerative Disorders, Hertie Institute of Clinical Brain Research, University of Tübingen, Tübingen, Germany

C. Schrader
Department of Neurology, University of Hannover, Hannover, Germany

Introduction

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder that usually manifests in the early sixth decade of life and progresses relentlessly with a mean survival of 9 years (Geser and Wenning 2006). MSA is clinically characterised by autonomic failure, which is associated with either levodopa-unresponsive parkinsonism in 80% (MSA-P subtype) or with cerebellar ataxia in 20% of cases (MSA-C subtype) (Wenning and Geser 2003). Although cardiovascular (e.g. orthostatic hypotension) and urogenital (e.g. incontinence) symptoms dominate the clinical picture (Ziemssen et al. 2006; Friedrich et al. 2008; Schmidt et al. 2008; Ziemssen and Reichmann 2010b), the usually neglected vasomotor system seems to be frequently involved as well (Asahina et al. 2003; Ziemssen and Reichmann 2010a). Consequently, MSA patients often feature cold, dusky and violaceous hands with poor circulatory return upon application of pressure. The so-called cold hand sign (CHS) is thought to be distinctive for MSA

since CHS has rarely been diagnosed in other parkinsonian syndromes (Klein et al. 1997). However, only a subgroup of MSA patients presents with CHS. This is important for differential diagnosis because MSA is still frequently misdiagnosed as idiopathic Parkinson's disease (PD). Because CHS is not life debilitating like dysautonomia of the urogenital system or other symptoms, it is barely receiving any consideration. Consequently, the underlying pathology of CHS is rather poorly understood.

To gain more insight into the pathophysiology of CHS, we performed quantitative evaluation of skin perfusion in MSA patients with CHS (MSA + CHS) and without CHS (MSA – CHS) in comparison to PD patients.

Patients and methods

Patients

Twenty-four patients with MSA were prospectively studied and compared with 12 PD patients between 2002 and 2005 at the Department of Neurology of the Universities of Dresden and Tübingen, Germany. The clinical diagnosis of MSA and PD was based on the criteria proposed by Gilman et al. (1998) and the UK Brain Bank Criteria (Hughes et al. 1992), respectively. Patients were excluded when a clear differential diagnosis could not be made based on the above criteria. All participants received oral and written information about the objectives and study procedure, and signed written informed consents prior to their inclusion into the study. At enrolment, all patients underwent a thorough neurological examination. Patients on vasoactive drugs were not included in the study. The MSA group included six MSA patients with CHS of their upper limbs as evaluated by clinical examination and documented by photography according to Klein et al. (1997). Disease severity was assessed according to the criteria proposed by Hoehn and Yahr (1967). Details on disease duration, disease severity and pharmacological treatment at the time of examination are given in Table 1. The study was approved by the Local Ethics Committee and confirmed with the principles of the Helsinki declaration.

Methods

All studies were performed in a temperature-controlled (20°C room temperature) autonomic laboratory in the morning. Ambient noise was kept to a minimum for the duration of testing. Oral temperature was initially measured with a digital thermometer. Skin blood flow (SBF) and skin temperature (ST) were measured using laser Doppler flowmetry (PeriFlux 5000/5010, Perimed, Stockholm, Sweden). This method utilizes fibreoptics to direct a laser light (780 nm wavelength) directly at the skin surface. The light is reflected back to the recording element of the probe from red blood cells in the skin capillaries (Lima and Bakker 2005). The wavelength of the reflected light is altered by the Doppler shift effect, caused by the movement of the red blood cells relative to the probe. This modified wavelength is then used to calculate an arbitrary perfusion rate (relative perfusion units, PU). Cutaneous vasodilation is apparent, as increase in perfusion units is relative to baseline perfusion.

With the patient in supine position, Doppler probes were attached to both index finger tips (pulp). Following a 20-min period of continuous basal recording, the probe was heated to a local temperature of 42°C within 20 s and maintained at this temperature for 10 min until blood flow did not change any more. The increment in temperature evokes maximal local vasodilation, thereby increasing local blood flow and skin temperature. SBF and ST data were stored for later analysis using PeriSoft for Windows software (Perimed, Stockholm, Sweden).

Statistical analysis

SPSS software package version 11.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical evaluations. Continuous data are presented as median and 25th–75th percentile unless otherwise stated. Categorical and nominal data are given as relative frequencies. Owing to the small sample size, we assumed non-Gaussian distribution and hence applied non-parametric tests (Mann–Whitney U Test) with Bonferoni correction for comparing independent means. Nominal data were compared by cross-tabulation using Fisher exact test. A two-tailed $p < 0.05$ was regarded as the level of statistical significance.

Results

The patient groups did not differ with regard to age, disease duration, disease severity, use of dopaminergic medication and oral temperature (Table 1). There were no differences regarding the prevalence and severity of autonomic dysfunction in MSA + CHS and MSA – CHS patients (patient questionnaire, Valsalva manoeuvre Schmidt et al. 2009), metronomic breathing, orthostatic hypotension). Figure 1 and Table 2 depict the results of skin perfusion testing: basal (non-stimulated) ST at the finger tips was significantly lower in MSA + CHS patients than in PD patients ($p < 0.018$), but did not differ in MSA – CHS patients. Basal (non-stimulated) SBF was lower in MSA patients irrespective of CHS compared to PD patients ($p < 0.006$). Maximal SBF in response to heating was significantly lower in MSA – CHS patients

Table 1 Clinical characteristics of patients with parkinsonian syndromes

	MSA – CHS	MSA + CHS	PD
Number of patients	18	6	13
Sex male/female (*N*)	8/10	2/4	9/4
Age at autonomic testing (years)	63.8 ± 7.4	61.3 ± 8.6	64.4 ± 6.2
Age at onset of disease (years)	58.3 ± 8.2	54.5 ± 9.0	53.0 ± 10.5
Duration of disease (years)	5.2 ± 2.7	6.8 ± 1.9	9.0 ± 5.2
Hoehn and Yahr staging	3.7 ± 1.1	4.3 ± 1.0	3.2 ± 0.7
Patients with medication	12	4	11
Levodopa	10	3	11
Mean daily dose in milligram	455 ± 241	900 ± 100	616 ± 469
Dopamine agonist	4	2	9
Pramipexole (mean daily dose in milligram)	2 (2.7 ± 0.1)	0	1
Pergolide (mean daily dose in milligram)	0	2 (3.0 ± 0)	3 (4.0 ± 2.6)
Cabergoline (mean daily dose in milligram)	2 (8.0 ± 0)	0	1
Ripinirole (mean daily dose in milligram)	0	0	4 (8.8 ± 7.9)
Bromocriptine	0	0	0
Dihydroergocriptine	0	0	0
Lisurid	0	0	0
MAO-B-inhibitor	1	0	2
COMT-inhibitor	3	0	2
Amantadine	5	3	1
Anticholinergics	1	0	0
Budipin	0	0	1
Dopaminergic medication	61% [11/18]	50% [3/6]	85% [11/13]
Body temperature (°C)	36.4 ± 0.3	36.4 ± 0.4	36.5 ± 0.3
Smoker	0% [0/18]	17% [1/6]	0% [0/18]

MSA multiple system atrophy, *CHS* cold hand sign, *PD* idiopathic Parkinson's disease

Data are given as mean ± standard deviation

than in MSA + CHS and PD patients ($p < 0.001$). The increase of SBF relative to basal SBP was significantly higher in MSA + CHS patients compared to MSA – CHS and PD patients ($p < 0.01$). Time to maximal ST during heating was longer in MSA + CHS and MSA – CHS patients in comparison to PD patients ($p < 0.01$) but time to maximal SBF did not differ between the groups. The SBF increment per temperature unit (1°C) was significantly lower in MSA – CHS patients compared to MSA + CHS patients ($p < 0.012$) but did not differ with regard to PD patients whilst SBF increment per time unit (1 s) was comparable in all three groups.

Discussion

The CHS presents a distinct feature in several, but not all MSA patients, but the underlying pathology is rather poorly understood. We, therefore, sought to characterise CHS in MSA to gain more insight into its pathology. This is the first study to show that maximal blood flow to local heating is increased in terms of kinetics and amplitude in MSA + CHS patients in comparison with MSA – CHS patients. PD patients served as control group since they do not present with CHS. While MSA + CHS patients differed from PD patients with regard to basal values and the relative change of SBF, kinetics of SBF was comparable between the two patient groups. These results suggest an impaired local temperature regulation during basal conditions in MSA + CHS, while local blood flow regulation to thermal stimuli is still intact. Although the latter appears to be altered in both MSA – CHS and PD patients, the magnitude of impairment seems to be greater in MSA – CHD patients. Klein et al. (1997) also investigated CHS in MSA by assessing ST before and after cooling the skin. In agreement with our results, they observed lower basal ST, greater reduction in ST after cooling and a prolonged recovery period in MSA patients compared to PD patients and healthy subjects. Another study in MSA patients assessed skin vasomotor function in response to local heating and revealed reduced amplitude of skin blood flow to heating compared to healthy subjects (Yamanaka et al.

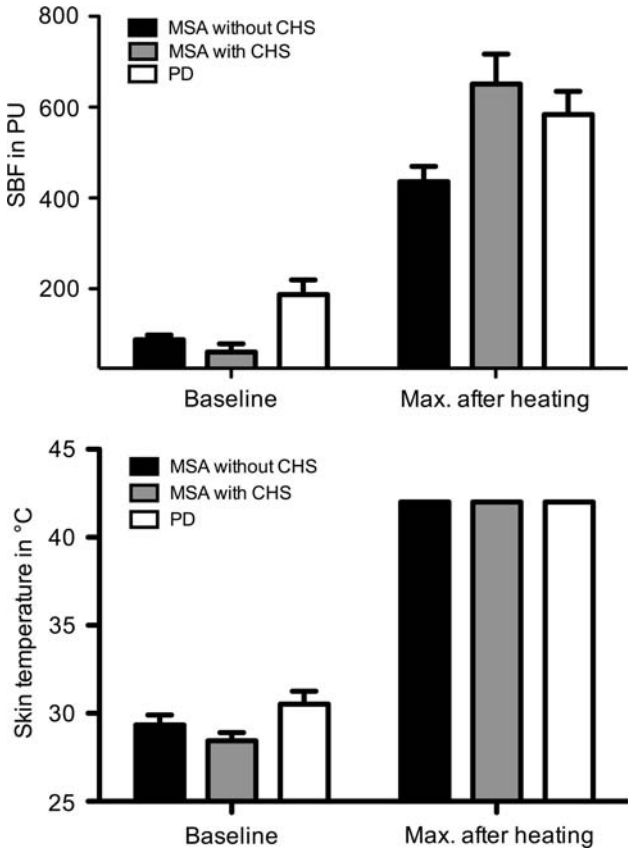

Fig. 1 (*Upper part*) Baseline skin blood flow and the maximum skin blood flow after heating for all patient groups. (*Lower part*) Baseline skin temperature and the maximum skin temperature after heating for all patient groups, Data are given as mean ± standard deviation. *MSA* multiple system atrophy, *CHS* cold hand sign, *PD* idiopathic Parkinson's disease, *ST* skin temperature, *SBF* skin blood flow

2007). Comparison of results is complicated because the investigators did not assess the presence of CHS in the investigated patients, and we were lacking a healthy control group. Two other studies assessed skin vasomotor reflex to various stimuli other than thermal in MSA patients and found either no or little difference compared to healthy subjects (Asahina et al. 2003; Young et al. 2006). The discrepancy to our results may be due to different mechanisms activated by the various stimuli. The skin vasomotor reflex responses to the emotional stimuli applied in those studies have been shown to require intact peripheral sympathetic function (Netten et al. 1995), whilst vasomotor response to heating is probably mediated by local mechanisms (Magerl and Treede 1996).

Local heating of glabrous skin has been suggested to increase blood flow through various pathways. Current knowledge allows differentiation of two phases, with the first phase featured by an early transient peak and a brief nadir followed by a progressive rise reaching a plateau at 30 min (phase 2) (Kellogg et al. 1999, 2003). While partial involvement of endothelial nitric oxide synthase pathway in the second phase has been evidenced by several groups (Kellogg et al. 1999, 2003; Gooding et al. 2006) the proposed activation of sensory axon reflex via C fibre nociceptors with the release of the neuropeptides substance P and gene-related peptide during the first phase of the response (Magerl and Treede 1996) is controversially discussed. We only analyzed the first phase response in our patients since abnormalities in MSA usually appear in this phase (Yamanaka et al. 2007). Our findings suggest a lower first phase response in MSA – CHD and PD patients in comparison with MSA + CHD patients presenting with apparent basal microcirculatory disturbance.

Still our study suffers from limitations which should be addressed. As mentioned earlier, we only analyzed the first phase of the skin vasomotor response to heating. Thus, we cannot rule out any changes or differences in the second phase. Furthermore, the small sample size precluded us from studying drug effects and also did not permit adjustment for possible confounders (e.g. smoking, disease duration and severity, age). Sub-analysis did not reveal any differences in group characteristics (Table 1). Moreover, differential diagnosis of possible MSA and PD was based on published clinical diagnostic criteria. As yet, definite confirmation of disease subtype requires postmortem analysis which, needless to say, was not possible.

Table 2 Skin vasomotor function pre - and post-local heating by patient groups

	MSA – CHS	MSA + CHS	PD
Absolute SBF increase (PU)	302.7 (203.1;448.8)[a]	595.1 (455.7;709.6)[b]	405.3 (280.9;521.0)[a]
Relative SBF increase (%)	442 (207;1187)[a]	1554 (635;3942)[b]	176 (124;937)[a]
SBF increment by temperature (PU/°C)	22.6 (12.4;31.7)[a]	36.3 (27.8;48.7)[b]	28.4 (15.4;39.4)[ab]
Time to maximal SBF (s)	102.2 (76.7;118.5)[a]	101.7 (87.8;124.6)[a]	68.6 (57.6;108.4)[a]
Time to maximal ST (s)	21.6 (17.9;24.8)[a]	22.3 (18.7;24.0)[a]	15.4 (13.9;19.8)[b]
SBF increment by time (PU/s)	3.6 (2.4;5.4)[a]	5.4 (3.8;8.0)[a]	4.5 (3.8;7.4)[a]

MSA multiple system atrophy, *CHS* cold hand sign, *PD* idiopathic Parkinson's disease, *ST* skin temperature, *SBF* skin blood flow

Data are given as median (interquartile range); unequal letters indicate differences between groups (Mann–Whitney *U* Test with Bonferroni correction)

Therefore, misclassification cannot be fully ruled out. As additional limitation, no parallel healthy control group was included in this trial.

Conclusion

Unlike MSA – CHS patients, MSA + CHS patients are characterised by intact skin vasomotor response to local heating despite impaired basal vasomotor function.

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