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Short communication

Alterations in electrochemical skin conductance as a marker of autonomic dysfunction in multiple system atrophy☆

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ABSTRACT

Background: Multiple System Atrophy (MSA) is a rare neurodegenerative disease with pronounced autonomic failure (AF). Severe cardiovascular AF is associated with poor prognosis. Since sweating dysfunction is less well known, we investigated the interest of a quick and non-invasive assessment of sweating using electrochemical skin conductance (ESC) as a marker for AF in MSA.

Methods: 138 MSA patients of the French Reference center for MSA with an annual follow-up including the Unified MSA Rating Scale (UMSARS), COMPASS (autonomic symptoms) and measurements of foot and hand ESC (Sudoscan®) participated to this study (age 65 ± 8 years, 66% probable MSA, 72% AMS-P). Statistical analysis included: (i) correlations between ESC and MSA type, age, disease duration, severity, blood pressure (BP), COMPASS, (ii) comparisons between groups with normal or abnormal ESC, and (iii) multivariate analysis by logistic regression. Relationships between severity progression during follow-up with ESC and other variables were modeled by Generalized Estimating Equation.

Results: Hands and feet ESCs were abnormal in 81/138 (59%) and 93/138 (67%) cases, respectively. Abnormal ESCs were significantly correlated to disease severity and several features of AF. ESCs worsening over time was more pronounced than other autonomic features such as orthostatic hypotension. Abnormal ESCs at baseline were significantly associated with a higher progression of UMSARS's score during follow-up.

Conclusion: Sweating dysfunction assessed by ESC is frequent in MSA and is significantly related to disease severity and AF. The gradual decrease in ESC with disease duration could be useful as a quantitative marker of autonomic dysfunction.

1. Introduction

Multiple System Atrophy (MSA) is a rare, sporadic, and progressive neurodegenerative disorder characterized by poorly levodopa-responsive parkinsonism and/or cerebellar ataxia, along with autonomic failure. Autonomic dysfunction is a key feature of current diagnosis criteria [1,2] and is believed to be linked to degeneration of preganglionic autonomic neurons of the brainstem and the spinal cord [3]. Although orthostatic hypotension (OH) and urinary dysfunction are known to be the two most common symptoms related to autonomic

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failure, recent evidence has shown that sudomotor dysfunction is almost always present in MSA [4]. Indeed sweat function assessment combined with cardiovascular autonomic testing can help to distinguish MSA-P from Parkinson's disease (PD) with autonomic failure [5]. Sweat glands are innervated by unmyelinated cholinergic sympathetic C-fibers. SUDOSCAN® is a quick and noninvasive technique that provides quantitative assessment of sweating based on electrochemical skin conductance (ESC) of hands and feet. Thus, our aim was to explore sweating alterations and their progression with time in patients with MSA, as assessed by ESC measurements.

2. Methods

2.1. Patient inclusion and follow-up

We retrospectively included 138 consecutive patients who were referred to the French MSA reference center (Toulouse site). To be included, patients had to meet the criteria for a diagnosis of probable or possible MSA [1,2], and to have at least one ESC measurement, as part of the autonomic evaluation. Patients were classified into MSA-P and MSA-C subtypes based on their predominant motor symptoms. Patients suffering from diabetes mellitus were excluded.

All patients provided written informed consent and the study was carried out in accordance with the declaration of Helsinki. These patients are part of a prospective longitudinal natural history cohort that has been registered with the CNIL (Commission Nationale Informatique et Liberté no.1338780; CCTIRS, no. 10.065). Follow-up data up to 24 months were studied in 18 patients.

2.2. Clinical and cardiovascular evaluation

Clinical assessment was performed using standardized scales for MSA (Unified Multiple System Atrophy Rating Scale, UMSARS [6]) and autonomic symptoms (COMPASS 31 [7]). To assess the severity of the disease, UMSARS I and II were added (UMSARS I + II) ranging from 0 to 104, with higher scores indicating a more severe illness. Blood pressure (BP) was measured in supine position every minute during 10 min in upright position to detect OH [8]. We calculated the maximum difference between supine systolic BP and standing systolic BP (ΔSBP), and between supine and standing diastolic BP (ΔDBP). Patients did not change their usual medication.

2.3. Electrochemical skin conductance assessment

To study sweating function, mean ESCs of both feet (F-ESCs) and both hands (H-ESCs) were assessed using Sudoscan® (Impeto medical, Paris, France). The method has been previously described [9] and relies on electrochemical skin reaction between sweat chloride and stainless steel electrodes on which a low painless direct current is applied. H-ESCs or F-ESCs thresholds for abnormal sudomotor function were defined as values < 60 μS or <70 μS respectively, as formerly defined in a large cohort of healthy individuals [9]. ESCs does not significantly vary with age until the 8th decade. Treatments with anticholinergic agents may influence ESCs and were taken into account in the statistical analysis.

2.4. Statistical analysis

Data are shown as means ± deviations or n (frequencies), except when otherwise indicated. Bivariate comparisons were performed by *t*-test, ANOVA, or chi-sq test. Correlations between ESCs and other variables were assessed by the Pearson method. Progression of UMSARS I + II score, COMPASS 31 score, BP fall after standing up, and ESCs during the 2-year follow-up period were assessed by General Estimating Equations (GEE). Sex, age, and disease duration were included as covariates. Multicollinearity was ruled out. Least-squares (LS) means and standard errors were calculated from the model. Post-hoc comparisons of least-squares means between groups were performed by the Bonferroni method. All analyses were performed by SPSS v22 (NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

One-hundred and thirty-eight patients were included in this study (mean age 65 ± 8 years); 65 patients (47%) were males. The predominant subtype was MSA-P in 99 patients (72%) and 91 patients (66%) had probable MSA. Mean disease duration from symptom onset was 4.8 ± 2.2 years. At baseline, mean UMSARS I + II score was 47.7 ± 14.7. Mean scores on the UMSARS' autonomic items were as follows: orthostatic symptom 1.48 ± 0.95, urinary function 2.72 ± 0.75, sexual function 3.57 ± 0.97 and bowel function 1.67 ± 0.86. Mean COMPASS 31 score was 15.0 ± 19.3. Thirty-four (25%) patients had moderate OH (defined as drop in SBP ≥20 mmHg or in DBP ≥10 mmHg), 57 (41%) severe OH (ΔSBP ≥30 mmHg or ΔDBP ≥15 mmHg), and 31 (22%) no OH.

3.1. Electrochemical skin conductance at baseline

F-ESCs and H-ESCs in the 138 patients were 59.5 ± 20.7 μS and 50.7 ± 19.7 μS, respectively. These values were abnormal in 81 (59%) and 93 (67%) cases, respectively. In 70 patients (51%), both F-ESCs and H-ESCs were abnormal. Thirty-four patients (25%) had abnormal ESCs in one site only (F-ESCs or H-ESCs), and 34 patients (25%) had normal ESCs. ESCs did not differ between MSA-P and MSA-C (F-ESCs: MSA-P = 59.6 μS and MSA-C = 59.4 μS ($p = 0.96$); H-ESCs: MSA-P = 50.5 μS and MSA-C = 51.2 μS ($p = 0.84$)). ESCs were not significantly correlated to age (F-ESCs: $r = -0.16$ ($p = 0.06$), H-ESCs: $r = -0.10$ ($p = 0.23$)). We observed a significant correlation between F-ESCs and H-ESCs and disease severity measured by UMSARS I + II ($r = -0.57$ $p < 0.01$ and $r = -0.52$ $p < 0.01$, respectively). Correlations between ESCs and autonomic variables are provided in Table 1. ESCs were significantly correlated to SBP drop in upright position ($r = -0.26$, $p < 0.01$), to mean total COMPASS score ($r = -0.35$, $p < 0.01$), and to UMSARS' autonomic items (urinary symptoms: $r = -0.38$ $p < 0.01$, sexual symptoms: $r = -0.28$ $p < 0.01$, gastrointestinal symptoms: $r = -0.27$, $p < 0.01$). In the multivariate regression analysis, only the SBP change after standing up remained significantly associated with ESCs.

3.2. Electrochemical skin conductance and blood pressure changes during follow-up

Eighteen of the 138 patients had at least one visit during the first and the second year of follow-up in addition to baseline (mean age 67.6 ± 7.7 years; 59% female; 59% probable MSA; 67% MSA-P). Mean UMSARS I + II at baseline was 39.4 ± 11.

Progression of UMSARS I + II score, COMPASS 31 score, BP changes after standing up, and ESCs are shown in Table 2. ESCs decreased on average by 15% after the first year of follow-up, and by 37% after the second year compared to baseline. These changes were statistically significant ($p < 0.01$). Although no major changes were observed during follow-up in DBP drop after standing, SBP drop increased by 38% during the first year of follow up, and 26% during second year compared to baseline ($p < 0.01$). Only the SBP variation at year 1 was significantly greater than baseline. The mean level of UMSARS I + II significantly increased after two years of follow-up from 42.6 ± 3.35 to 58.1 ± 4.36 ($p < 0.01$). The increase in COMPASS 31 score with time was not significant.

At baseline, 6 patients (33%) had normal ESCs and 12 (66%) had abnormal F-ESCs and/or H-ESCs. Compared to patients with normal ESCs, those with abnormal ESCs tended to have a higher average UMSARS I + II score (45.5 ± 4.3, vs. 37.2 ± 3.3, $p = 0.11$). Worsening of the UMSARS I + II score was significantly greater in patients with abnormal baseline ESCs compared to those with normal ESCs (from 45.5 ± 4.3 to 62.1 ± 5.0 at year 2, vs from 37.2 ± 3.3 to 50.8 ± 7.2, $p < 0.01$).

Table 1
Correlations between Electrochemical Skin Conductance (ESC) and autonomic dysfunction parameters.

	Foot ESC		Hand ESC		Mean ESC	
	Bivariate r coefficient	Multivariate st. β coef	Bivariate r coefficient	Multivariate st. β coef	Bivariate r coefficient	Multivariate st. β coef
Blood pressure measurements						
SBP (supine)	−0.13	–	−0.17	–	−0.16	–
DBP (supine)	−0.14	–	−0.07	–	−0.12	–
HR (supine)	−0.07	–	−0.07	–	−0.08	–
ΔSBP (orthostatism)	−0.23*	−0.19*	−0.25**	−0.24**	−0.26**	−0.23**
ΔDBP (orthostatism)	0.16	–	0.13	–	0.16	–
ΔHR (orthostatism)	−0.05	–	0.01	–	−0.02	–
UMSARS autonomic items (9–12)						
Orthostatic symptoms	−0.14	–	−0.12	–	−0.14	–
Urinary function	−0.33**	–	−0.37**	–	−0.38**	–
Sexual function	−0.18*	–	−0.34**	–	−0.28**	–
Bowel function	−0.24**	–	−0.26**	–	−0.27**	–
COMPASS 31 scores						
Orthostatic hypotension	−0.29**	−0.16	−0.24**	−0.05	−0.29**	−0.12
Vasomotor	−0.12	0.06	−0.10	0.11	−0.11	0.09
Secretomotor	−0.20*	0.01	−0.23**	−0.01	−0.23**	−0.01
Gastrointestinal	−0.31**	−0.18	−0.30**	−0.26	−0.33**	−0.24
Urinary	−0.31**	−0.13	−0.25**	−0.03	−0.30**	−0.06
Pupillomotor	−0.23**	0.03	−0.20*	−0.09	−0.23**	−0.03
Total score	−0.34**	–	−0.30**	–	−0.35**	–

*p < 0.05, **p < 0.01 (*t*-test).
Foot ESC: mean value of both feet –**Hand ESC**: mean value of both hands – **Mean ESC**: mean value of both feet and both hands**. SBP**: systolic blood pressure, **DBP**: diastolic blood pressure, **HR**: heart rate, **ΔSBP**: maximum SBP variation between supine and standing position, **ΔDBP**: DBP maximum variation between supine and standing position, **ΔHR**: HR between supine HR and last standing HR.

Table 2
Progression in 18 MSA patients during the 2-year follow-up period.

	Baseline (n = 18)	Year 1 (n = 18)	Year 2 (= 18)	Overall p-value*
UMSARS I + II	42.6 ± 3.35	52.4 ± 3.63[a]	58.1 ± 4.36[ab]	<0.01
COMPASS 31 score	19.1 ± 4.4	28.2 ± 5.0	32.3 ± 5.8	0.16
ΔSBP (orthostatism)	−25.0 ± 3.72	−36.2 ± 5.58[a]	−29.5 ± 4.19	0.03
ΔDBP (orthostatism)	−6.0 ± 1.38	−7.9 ± 1.78	−7.5 ± 1.83	0.71
Feet ESC (μS)	68.4 ± 6.74	55.4 ± 4.91	39.2 ± 5.15[ab]	<0.01
Hands ESC μ S)	46.1 ± 4.07	41.8 ± 4.26	31.1 ± 4.50[ab]	<0.01
Mean ESC (μ S)	57.0 ± 4.83	48.9 ± 4.03	35.7 ± 4.53[ab]	<0.01

LS means as calculated by the GEE model are shown. * Post hoc comparisons were adjusted by Bonferroni method ([a] p < 0.05 vs baseline; [b] p < 0.05 vs Year 1). **ΔSBP**: SBP maximum variation between supine and standing position, **ΔDBP**: SBP maximum variation between supine and standing position, **ESC**: electrochemical skin conductance.

Patients with abnormal ESCs had a larger fall in SBP after standing up at baseline and follow-up visits compared to those without ESCs abnormalities (systolic BP drop at baseline: -28.9 ± 5.0 vs −17.2 ± 2.9, systolic BP drop at year 2: -32.7 ± 4.3 vs. −18.7 ± 6.0, $p = 0.05$). Concerning autonomic symptoms, COMPASS 31 score at the first visit did not differ between patients with or without abnormal ESCs (17.7 ± 3.5 vs. 18.8 ± 5.1, $p = 0.69$).

4. Discussion

To our knowledge, this study is the first to provide a characterization of sweating dysfunction in MSA using ESC assessment. One main finding is a significant correlation between ESCs and the severity of both disease and different markers of autonomic dysfunction.

At their first visit, 70% of patients had abnormal F-ESC or H-ESCs. This supports the idea that, although few patients complain of symptoms related to anhidrosis, sweat dysfunction is common in MSA. Our findings are consistent with those of Coon et al., who reported abnormal post-ganglionic sudomotor testing (using quantitative sudomotor axon reflex testing (QSART)) in 59% and abnormal thermoregulatory sweat test (TST) in 95% of patients (TST anhidrosis >40% in 64%) at initial evaluation (mean disease duration 3.36 years) [4]. Moreover, a recent study using skin biopsy from the distal leg showed that patients with early MSA-P had reduced pilomotor and sudomotor nerve density compared to both controls and patients with PD. Pilomotor and sudomotor nerve densities were correlated with both postganglionic sudomotor function and nonmotor symptoms [10]. Together with our findings, this suggests that ESC could be a reliable marker to assess sweat function in patients with MSA even though this measurement does not determine whether the involvement is pre- or post-ganglionic.

We observed a significant association between sweating dysfunction and disease severity as assessed by the UMSARS I + II score. F-ESCs and H-ESCs were also significantly related to the drop in SBP after standing and to autonomic symptoms as evaluated with two clinical scales (COMPASS 31 and UMSARS (autonomic items)). This suggests that initial ESCs may reflect the severity of both disease and autonomic dysfunction. Among the 18 patients who had more than one assessment, those with abnormal ESCs at baseline tended to have a higher average UMSARS I + II score with a significantly greater worsening compared to those with normal ESCs. It has already been demonstrated that early severe autonomic failure, in particular OH or urogenital dysfunction, is associated to faster disease progression [11]. Major autonomic failure and disease severity (UMSARS I + II score) at the first visit have been considered as negative prognostic factors [11,12]. In this respect, our findings suggest that altered F-ESC and H-ESCs at baseline may predict more severe disease with faster progression over time. These results have to be confirmed in a larger cohort of MSA patients followed over a longer period of time.

Regarding the progression of autonomic symptoms, we found a tendency for the COMPASS 31 score to worsen over time, but this was not significant. Similar to previous studies conducted in large populations, the decrease in SBP after standing worsened moderately over time [11]. However, the most remarkable change was observed for ESC values. Our finding of a gradual decrease in ESC values with the disease duration is consistent with the observations reported by another study

using QSART in patients with MSA [4].

One limitation is that data were collected retrospectively and only a small proportion of patients had more than one assessment of sweating dysfunction. Another limitation of this study is the lack of autopsy-confirmed diagnosis of MSA in deceased patients.

In conclusion, our study provides an evaluation of sweating dysfunction using ESC, a quick and noninvasive technique which is convenient for longitudinal follow-up of patients and which can easily be implemented in clinical routine. We observed a significant correlation between ESCs and other measures of autonomic dysfunction, in particular the SBP drop after standing, in patients with MSA. Although the profile of worsening during the follow-up of ESC values must be characterized more precisely, our results suggests that ESC could be a quantitative marker for autonomic failure progression in MSA.

Declaration of competing interest

None.

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