Progression of dysautonomia in multiple system atrophy: a prospective study of self-perceived impairment

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To assess severity and progression of self-perceived dysautonomia and their impact on health-related quality of life (HR-QoL) in multiple system atrophy (MSA), twenty-seven patients were recruited by the European MSA Study Group (EMSA-SG). At baseline, all patients completed the Composite Autonomic Symptom Scale (COMPASS) and the 36 item Short Form Health Survey (SF-36), and they were assessed using the 3-point global disease severity scale (SS-3) and the Unified MSA Rating Scale (UMSARS). After 6 months follow-up, the self-completed COMPASS Change Scale (CCS), the SF-36, SS-3, and UMSARS were obtained. MSA patients showed marked self-perceived dysautonomia at baseline visit and pronounced worsening of dysautonomia severity on the CCS at follow-up. Severity and progression of dysautonomia did not correlate with age, disease duration, motor impairment and overall disease severity at baseline. There were no significant differences between genders and motor subtypes. Baseline COMPASS scores were, however, inversely correlated with SF-36 scores. Progression of self-perceived dysautonomia did not correlate with global disease progression. HR-QoL scores were stable during follow-up. This is the first study to investigate self-perceived dysautonomia severity in MSA and its evolution over time. Our data suggest that dysautonomia should be recognized as a key target for therapeutic intervention in MSA.

Introduction

Multiple system atrophy (MSA) is a fatal progressive neurodegenerative disorder characterized by multisystem neuronal loss, gliosis and abnormal \( \alpha \)-synuclein aggregation in oligodendroglia and neurons [1,2]. Clinically, the cardinal features include autonomic failure, parkinsonism, cerebellar ataxia and pyramidal signs in any combination [3]. In Western populations, parkinsonian features predominate in 80\% of patients (MSA-P subtype), and cerebellar ataxia is the main motor feature in 20\% of patients (MSA-C subtype). Dysautonomia including orthostatic hypotension and urogenital dysfunction occurs in both motor subtypes [4]. Although, the dynamic evolution of motor impairment and its severity in MSA has been investigated prospectively [4–6], there is only retrospective information on the severity and time course of dysautonomia in this disorder [7–9]. In the present study, we used the Composite Autonomic Symptom Scale (COMPASS) [10], a self-completed and validated questionnaire to assess the subjective severity of dysautonomia in MSA, and the COMPASS Change Scale (CCS), a new instrument based on the COMPASS, to prospectively assess its progression.

Methods

Patients

We studied 27 patients with a clinical diagnosis of probable MSA recruited at four centres of the European MSA Study Group (EMSA-SG). A summary of their clinical characteristics is given in Table 1. Patients were included as part of a natural history study of MSA and had to fulfil the consensus criteria for possible or probable MSA [3]. All patients received a baseline assessment comprising basic demographic and clinical
data as well as a range of scales including the COMPASS scale [10], the 3-point global disease severity scale (SS-3) [11], and the 36 item Short Form Health Survey (SF-36) [12] to assess Health-related Quality of Life (Hr-QoL).

At 6 months follow-up, the COMPASS Change Scale (CCS, see Appendix), the SF-36, and both the SS-3 and UMSARS were administered. Blood pressure change to active standing for 2 min was measured at both visits. The study was approved by the local ethics committees.

### Instruments

The COMPASS is a validated, self-completed 169 item questionnaire [10]. Seventy-three questions assess the following nine domains of autonomic symptoms: orthostatic, secretomotor, male sexual dysfunction, urinary, gastrointestinal, pupillomotor and vasomotor function, reflex syncope and sleep function. These items are scored based on presence, severity, distribution, frequency and progression of symptoms. This scale was used as it was the only available self-reported scale to assess autonomic dysfunction in MSA at the beginning of the study.

The CCS is based on the COMPASS scale modified for the quantitative assessment of progression of dysautonomia. It comprises 26 retrospective questions divided into change of six autonomic function domains [i.e. orthostatic intolerance, sexual failure (erectile dysfunction, male only), bladder disorder, secretomotor disorder, constipation and sleep disorder] with a maximum score of 160 for men and 150 for women, indicating fastest progression (Fig. 1). To reduce the extensive COMPASS questionnaire, several items such as vaso- and pupillomotor dysfunction were not included in the CSS. The CSS will be fully validated during the EMSA-SG natural history study using repeated cardiovascular autonomic and urodynamic function tests [13]. The current work represents an intermediate report with 6 months follow-up and full validation data will become available in approximately 2 years time.

The UMSARS is a recently developed and validated scale [11] for assessing disease severity in MSA. The scale comprises the following components: part I, activities of daily living (ADL), 12 items; part II, motor examination, 14 items; part III, autonomic examination; and part IV, global disability scale. Summary scores can be calculated for part I, II and IV. Higher scores on the UMSARS scale indicate greater disease severity. The UMSARS has already been validated longitudinally showing its ability to detect progression of disease severity [14]. The SS-3 is a simple physician-rated 3-point [mild (1) – moderate (2) – severe (3)] global disease severity scale that correlates significantly with all UMSARS subscores and other global disease severity scales, i.e. Hoehn and Yahr and Schwab and England Scale [11]. The SF-36 [12] represents a widely used health measure that assesses several domains of health (physical and social functioning, physical and emotional role limitations, mental health, energy, pain and general

### Table 1 Patient characteristics (n = 27)

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>18</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>MSA-P</td>
<td>17</td>
<td>63</td>
</tr>
<tr>
<td>MSA-C</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Orthostatic symptoms</td>
<td>19</td>
<td>70</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>13</td>
<td>48</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>13</td>
<td>48</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Mean (median)</th>
<th>SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60</td>
<td>8.8 (47–80)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>5.2</td>
<td>3.6 (1–16)</td>
</tr>
<tr>
<td>SS-3 (BL)</td>
<td>2.24 (2)</td>
<td>0.7 (1–3)</td>
</tr>
<tr>
<td>SS-3 (FU)</td>
<td>2.43 (2)</td>
<td>0.6 (1–3)</td>
</tr>
<tr>
<td>UMSARS-ADL part (BL)</td>
<td>22.5 (20)</td>
<td>8.6 (12–38)</td>
</tr>
<tr>
<td>UMSARS-ADL part (FU)</td>
<td>25.45 (25.5)</td>
<td>9.8 (9–42)</td>
</tr>
<tr>
<td>UMSARS-motor part (BL)</td>
<td>24.9 (24)</td>
<td>8.7 (12–45)</td>
</tr>
<tr>
<td>UMSARS-motor part (FU)</td>
<td>28.1 (28)</td>
<td>10.4 (12–47)</td>
</tr>
<tr>
<td>UMSARS global disability part (BL)</td>
<td>3.11 (3)</td>
<td>1.2 (1–5)</td>
</tr>
<tr>
<td>UMSARS global disability part (FU)</td>
<td>3.41 (3.5)</td>
<td>1.05 (1–5)</td>
</tr>
</tbody>
</table>

MSA, multiple system atrophy; P, parkinsonian; C, cerebellar ataxia; SS-3, 3-point global disease severity scale; UMSARS, Unified MSA Rating Scale; ADL, activities of daily living; BL, baseline; FU, follow-up.

aBlood pressure drop of more than 30 mmHg systolic or 15 mmHg diastolic; bblood pressure drop of more than 20 mmHg systolic or 10 mmHg diastolic.

The CCS shows median, interquartile distance, and range of CSS scores of the patients. The white boxes represent the range of possible values for the single subscore, positive values indicating worsening and negative values improvement of dysautonomia.
health perceptions), and a physical and mental summary score can be derived from these. The maximum score of 100 indicates the best possible health state.

The SF-36 is available in multiple languages. All other questionnaires used in this study were subjected to back- and forward-translation by professional translators before use.

### Statistical analyses

Scores and subscores of clinical scales were calculated according to the respective scoring algorithms. For statistical analysis data were tabulated and analysed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA). All data are expressed as mean (standard deviation, SD) or medians (range) depending on the data distribution. COMPASS scores were compared with a published age-matched control group [10]. Group differences of COMPASS and CCS scores between motor subtypes and genders were analysed by the Mann–Whitney test and associations between COMPASS or CCS scores with age, disease duration and other clinical scales with Spearman rank correlations. Scores at baseline and follow-up were compared using the Wilcoxon signed rank test. Correlations between Hr-QoL scores and COMPASS score were adjusted for UMSARS motor scores. A forward stepping linear regression analysis (significance level 5%), entering age, disease duration, global disease severity, UMSARS motor scores, and COMPASS total score was performed to determine which factors contribute to reduced Hr-QoL. Regression analysis was also performed to determine baseline predictors of a more pronounced progression of dysautonomia.

### Results

#### Clinical features

Seventeen patients fulfilled diagnostic criteria [3] of probable MSA-P, 10 of probable MSA-C (Table 1). More than two-third of the patients in this study reported orthostatic symptoms and 48% of the patients had orthostatic hypotension with a blood pressure fall of more than 30 mmHg systolic or 15 mmHg diastolic [3] and 60% with more than 20 mmHg systolic or 10 mmHg diastolic [15]. Urinary incontinence and/or urinary retention was present in half of the patients (Table 1).

#### Baseline visit

Multiple system atrophy patients showed higher COMPASS scores than a published normal control group [10] in most domains of autonomic symptoms including orthostatic hypotension, secretomotor function, male sexual dysfunction, urinary, pupillomotor and sleep function (Table 2). There was no significant difference between MSA-P and MSA-C patients. Women had a worse score than men only in the bladder subdomain (10.8 ± 6.3 vs. 5.3 ± 4.2; \( P = 0.02 \)). There were no correlations of COMPASS scores with age, disease duration, global disease severity (SS-3), motor impairment as measured on the UMSARS motor examination part, the UMSARS global severity score, the total UMSARS ADL part (\( r = 0.10, P = 0.65 \)) and the degree in systolic or diastolic blood pressure drop (data not shown).

Mean SF-36 physical and mental summary scores were substantially lower than in healthy controls [16,17], and similar to those found in patients with Parkinson’s disease [18]. SF-36 mental summary scores (\( r = -0.65, P = 0.006 \)) as well as physical summary scores (\( r = -0.57, P = 0.02 \)) at baseline correlated inversely and significantly with the COMPASS total score. COMPASS total scores correlated inversely and significantly with the following SF-36 subscores: vitality (\( r = -0.82, P < 0.001 \)), general health (\( r = -0.74, P = 0.001 \)) and mental health (\( r = -0.56, P = 0.03 \)). All correlations were adjusted for motor impairment as measured by UMSARS motor part. Regression analysis showed that COMPASS scores account for 45% of the variance of mental summary scores (\( R = 0.68, R = 0.46, P = 0.004 \)); motor scores (UMSARS motor part) did not contribute further.

#### Table 2 Composite Autonomic Symptom Scale scores compared with normal controls

<table>
<thead>
<tr>
<th>Domains</th>
<th>Maximal possible score</th>
<th>MSA ((n = 22))</th>
<th>Controls ((n = 41))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic intolerance</td>
<td>40</td>
<td>Mean: 18.2</td>
<td>Mean: 3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD: 11.2</td>
<td>SD: 0.9</td>
</tr>
<tr>
<td>Secretomotor</td>
<td>20</td>
<td>4.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Sexual dysfunction (M)</td>
<td>30 (M)</td>
<td>9.9</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>4.4 (F)</td>
<td>5.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Urinary</td>
<td>20 (M)</td>
<td>7.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Gastroparese</td>
<td>10 (M)</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>1.4 (F)</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>20 (M)</td>
<td>0.2</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>0.3 (F)</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (M)</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>2.4 (F)</td>
<td>3.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pupillomotor</td>
<td>5 (M)</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>3.4 (F)</td>
<td>4.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Vasomotor</td>
<td>10 (M)</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>1.0 (F)</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Reflex syncope</td>
<td>20 (M)</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>1.0 (F)</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Sleep</td>
<td>15 (M)</td>
<td>5.5</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>2.5 (F)</td>
<td>3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Total (M/F)</td>
<td>200/170</td>
<td>55.9/42.3</td>
<td>20.9/17.2</td>
</tr>
</tbody>
</table>

MSA, multiple system atrophy; M, male; F, female.

aNormal control data taken from Suarez et al.[10].bThe lowest possible score is 0 for all domains.
Follow-up visit

Drug therapy for dysautonomia remained unchanged throughout the follow-up period. The levodopa equivalent dose was also stable at follow-up (baseline 887.4 mg ± 638.8, follow-up 952.4 mg ± 600.5; \( P = 0.57 \)). Global disease severity (9%, \( P = 0.06 \)), UMSARS motor (13%, \( P = 0.06 \)) and ADL subscores (13%, \( P = 0.003 \)) progressed significantly compared with baseline. All but one patient (96%) showed worsening of autonomic symptoms as measured by CCS (Table 3, Fig. 1) over a period of 6 months. There was no significant difference of CCS between gender and motor subtypes. CCS scores correlated with age (\( r = 0.43, P = 0.025 \)) but not with disease duration (\( r = 0.002, P = 0.99 \)). Orthostatic systolic and diastolic blood pressure drop at 6 months follow-up did not significantly correlate with either total CSS score or the cardiovascular CSS subscore (data not shown).

There was no correlation between CCS scores and progression of global disease severity (SS-3), UMSARS motor scores sub-scores as well as SF-36 scores.

Regression analysis determined the COMPASS total score at baseline as a predictive factor for change in dysautonomia severity, accounting for 30% of the variance of CCS scores (\( R = 0.55, R^2 = 0.30, P = 0.02 \)). UMSARS motor scores at baseline did not contribute further.

There was no significant worsening of SF36 summary scores (physical summary score: baseline 31.9 ± 21.0, follow-up 26.9 ± 12.5, \( P = 0.49 \); mental summary score: baseline 43.8 ± 27.2, follow-up 48.9 ± 20.2 \( P = 0.74 \)) and as of SF-36 subscores after 6 months (data not shown).

Discussion

Dysautonomia is one of the cardinal features of MSA comprising a range of features including cardiovascular and urogenital failure [3,4,19–21] However, most natural history studies in MSA have focused on the nature and progression of motor impairment, whilst only limited data are available on dysautonomia [7,8,10,22] and its evolution [23]. In the present study, we therefore evaluated severity and prospective time course of self-perceived dysautonomia in MSA. We assessed this with the COMPASS, a self-completed scale of self-perceived dysautonomia severity, validated in patients with autonomic failure including MSA [10]. In order to evaluate the time course of dysautonomia we used the CSS, a new self administered questionnaire based on selected COMPASS items to assess change over time.

The results show that self-perceived dysautonomia in MSA is severe, particularly compromising orthostatic and urogenital function, confirming a previous smaller study [10]. A recently published study on 22 MSA patients [23] also shows that urogenital dysfunction is of early onset and particularly prominent in this disease. COMPASS scores at baseline did not correlate with age, sex and disease duration. These findings are not surprising as dysautonomia is often a presenting feature of MSA [4] and therefore correlations with age and disease duration may be found only at early disease stages. COMPASS scores did not correlate with measures of disease severity as measured on the motor, ADL and global disease severity parts of the UMSARS. This lack of correlation may partly reflect the subjective nature of COMPASS scores. However, it may also suggest that dysautonomia severity is dissociated from motor dysfunction as assessed by UMSARS.

Health-related quality of life was substantially reduced in this patient cohort as demonstrated previously [24]. Severity of dysautonomia was significantly related to the mental and physical summary score of SF-36. Dysautonomia accounted for 45% of the variance in the mental summary score. Motor function on the other hand did not account for a significant amount of its variance beyond that explained by the COMPASS scores. The linkage between dysautonomia and Hr-QoL has been established only recently [25] as clinical interest on dysautonomia in MSA has been focused on objective rather than subjective impact on patients’ life.
As no further reduction of Hr-QoL scores was observed during follow-up, it seems unlikely that CSS scores were biased by deterioration of quality of life.

Composite Autonomic Symptom Scale scores did not correlate with orthostatic blood pressure change at baseline. This observation suggests that subjective perception of orthostatic intolerance may not be adequately reflected by measurements of blood pressure change on standing in many patients with MSA [19]. Patients with neurogenic autonomic failure are reported to have high COMPASS subscores despite weak correlation with objective measures [10]. Therefore we recommend that blood pressure measurements should always be accompanied by an enquiry for subjective orthostatic intolerance.

All but one patient reported a worsening of the autonomic symptoms over the past 6 months as assessed by the CCS scores. The UMSARS motor score and the ADL scores changed by 13% and 16% but there was no correlation between CCS and change in motor or ADL scores. The highest change scores were seen in the orthostatic symptom and sexual function (males only) subdomains, followed to a lesser degree by bladder disorder. Progression of orthostatic intolerance reported by our patient group; however, was not reflected in blood pressure response to active standing up as no significant change to baseline could be detected. This is possibly because of the poor reproducibility of orthostatic blood pressure change [26], which therefore may be inadequate for natural history studies.

Our results are similar to those by Mabuchi et al. [23] who reported increased frequencies of urinary dysfunction and faintness with follow-up over more than 7 years in patients with MSA. Progression of severity of dysautonomia otherwise was not addressed in their study.

Composite Autonomic Symptom Scale Change Scale scores showed no correlation with progression of global disease severity (SS-3) and motor impairment (UMSARS motor part). This may suggest that these problems progress differentially, reflecting a considerable variability of neurodegenerative lesions in the central autonomic and motor pathway [22]. Further, clinical and clinicopathological studies are required to resolve the dynamic evolution of autonomic and motor dysfunction in MSA.

Based on the self-completed questionnaires COMPASS and CSS, we conclude that dysautonomia in MSA is severe and preferentially affects urinary and orthostatic dysfunction. It is also tightly associated with reduced mental health aspects of Hr-QoL, including vitality. Dysautonomia and its progression appears to be unrelated to age, sex, disease duration, global disease severity and motor impairment, and the progression of global and motor impairment. Further prospective studies are required to examine the possible dissociation of autonomic and motor dysfunction and their dynamic evolution in MSA. As dysautonomia contributes to reduced Hr-QoL, emphasis on this feature should therefore gain greater importance in the treatment of the disease.

References


3. Bladder disorder
3.1 Do you have problems with leakage of urine or losing control of your bladder function?
Since the last evaluation is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

3.2 Do you have difficulty passing urine?
Since the last evaluation is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

3.3 Do you have trouble completely emptying your bladder?
Since the last evaluation is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

4. Secretomotor disorder
4.1 Since your last evaluation, has your ability to sweat gotten much worse, somewhat worse, unchanged, somewhat better, much better?

4.2 Since your last evaluation, what changes, if any, have occurred in your ability to tolerate heat during a hot day, strenuous work or exercise, hot bath, or shower, hot tub, or saunas? Much worse, somewhat worse, unchanged, somewhat better, much better?

4.3 Do you have dry hands or dry mouth?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

Appendix: The COMPASS Change Scale (CCS)

1. Orthostatic intolerance
1.1 Comparing your symptoms now with your symptoms at the last evaluation, these symptoms on standing up, are getting better, worse, unchanged?
   a. rapid heart beat or feeling shaky
   b. nausea
   c. blurred vision
   d. cold and clammy hands
   e. difficulty thinking or concentrating
   f. head or neck ache
   g. chest pain or difficulty breathing

1.2 These symptoms brought on by, or made worse by the procedures below, are getting better, worse, unchanged since last evaluation
   a. activity or exercise
   b. hot bath, tub, sauna or hot shower
   c. soon after eating a meal
   d. after standing for a long time

1.3 Since the last evaluation, the time that you can stand up for is now much shorter, somewhat shorter, unchanged, somewhat longer, much longer?

1.4 Since the last evaluation, your energy level for physical activity is now worse, better, unchanged?

1.5 Your endurance level for physical activity is now worse, better, unchanged?

1.6 Since the last evaluation, the frequency that symptoms develop when you stand up is worse, better, unchanged?

2. Sexual failure (male only)
Since the last evaluation is your ability to have a full erection getting much worse, somewhat worse, unchanged, somewhat better, much better?

3. Bladder disorder
3.1 Do you have problems with leakage of urine or losing control of your bladder function?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

3.2 Do you have difficulty passing urine?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

3.3 Do you have trouble completely emptying your bladder?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

4. Secretomotor disorder
4.1 Since your last evaluation, has your ability to sweat gotten much worse, somewhat worse, unchanged, somewhat better, much better?

4.2 Since your last evaluation, what changes, if any, have occurred in your ability to tolerate heat during a hot day, strenuous work or exercise, hot bath, or shower, hot tub, or saunas? Much worse, somewhat worse, unchanged, somewhat better, much better?

4.3 Do you have dry hands or dry mouth?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?
5. Constipation
5.1 Do you have constipation?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

6. Sleep disorder
6.1 Do you have sleep apnea?
Since the last evaluation, is this difficulty getting much worse, somewhat worse, unchanged, somewhat better, much better?

6.2 Do you have snoring?
Since the last evaluation, is this difficulty getting worse, staying the same, getting better?

6.3 Compared with your last evaluation, how would you rate how refreshing and restorative your sleep is?
Much worse, somewhat worse, unchanged, somewhat better, much better?