Patient-perceived progression in multiple system atrophy: natural history of quality of life

Tiphaine Saulnier,1,2 Margherita Fabbri,3,2 Mélanie Le Goff,1 Catherine Helmer,1,4 Anne Pavy-Le Traon,3,2 Wassilios G. Meissner,5,6 Olivier Rascol,2,3 Cécile Proust-Lima,1,4,5

ABSTRACT

Background Health-related quality of life (Hr-QoL) scales provide crucial information on neurodegenerative disease progression, help improve patient care and constitute a meaningful endpoint for therapeutic research. However, Hr-QoL progression is usually poorly documented, as for multiple system atrophy (MSA), a rare and rapidly progressing alpha-synucleinopathy. This work aimed to describe Hr-QoL progression during the natural course of MSA, explore disparities between patients and identify informative items using a four-step statistical strategy.

Methods We leveraged the data of the French MSA cohort comprising annual assessments with the MSA-QoL questionnaire for more than 500 patients over up to 11 years. A four-step strategy (1) determined the subdimensions of Hr-QoL, (2) modelled the subdimension trajectories over time, (3) mapped item impairments with disease stages and (4) identified most informative items.

Results Four dimensions were identified. In addition to the original motor, non-motor and emotional domains, an oropharyngeal component was highlighted. While the motor and oropharyngeal domains deteriorated rapidly, the non-motor and emotional aspects were already impaired at cohort entry and deteriorated slowly over the disease course. Impairments were associated with sex, diagnosis subtype and delay since symptom onset. Except for the emotional domain, each dimension was driven by key identified items.

Conclusion The multidimensional Hr-QoL deteriorates progressively over the course of MSA and brings essential knowledge for improving patient care. As exemplified with MSA, the thorough description of Hr-QoL over time using the four-step strategy can provide perspectives on neurodegenerative diseases’ management to ultimately deliver better support focused on the patient’s perspective.

INTRODUCTION

Multiple system atrophy (MSA) is a rare, neurodegenerative and incurable disease characterised by a variable combination of parkinsonism, cerebellar impairment and autonomic disorders. The disease has a progressive and rapid global degradation, and a poor prognosis. In MSA as in other neurodegenerative diseases, health-related quality of life (Hr-QoL) is rapidly affected1–3 and strongly related to the disease process. Therefore, studying the disease progression with a focus on patients’ perception can provide crucial information on the disease course, giving clinicians opportunities to deliver better support.4,5 In recent years, Hr-QoL has been a key domain in the study of Parkinson’s disease used to adapt care planning.6–8 Supported by the WHO and the Food and Drug Administration, the assessment of Hr-QoL has become crucial for the improvement of care and drug development.9 However, the progression of Hr-QoL in MSA remains insufficiently documented.10 Beyond the disease rarity and availability of large cohorts, this deficit is explained by the statistical challenges raised by Hr-QoL data.

Hr-QoL is a complex concept, reflecting multiple aspects such as physical condition, psychological state and social relationships. It is usually assessed by Likert measurement scales composed of numerous items transcribing the disease manifestations experienced by patients with graded scores.6,8,11 Each item provides relevant information that needs to be accounted for, which prevents the use of sum scores.12 Moreover, the study of changes in Hr-QoL over time requires the use of statistical methods adapted to longitudinal data and to occurrence of events such as death, which interrupt the follow-up, inducing missing data, usually for
patients with highest impairments.\textsuperscript{13} Finally, in neurodegenerative diseases, the progression of Hr-QoL would benefit from being mapped against clinical progression to better understand the link between clinical and QoL impairments.

Based on the French MSA cohort, this work aimed to better understand QoL evolution during the natural disease course, identify factors associated with progression and relate progression to disease staging. For this purpose, we addressed the methodological challenges with a four-step statistical strategy to analyse longitudinal Hr-QoL data, applicable to any neurodegenerative disease.

**MATERIALS AND METHOD**

**Study population and materials**

The French MSA cohort was created in 2007 by the French Reference Centre, a collaboration between the University Hospitals in Bordeaux and Toulouse.\textsuperscript{1} Its constitution has been registered with the Commission Nationale Informatique et Liberté. It is an open and prospective cohort that includes all consenting patients diagnosed with MSA according to the Gilman criteria\textsuperscript{14} who undergo annual follow-ups with standardised clinical assessment. For this work, all inclusions and follow-up data prior to 31 December 2021 (called administrative censoring) were considered.

**Ascertainment of MSA-QoL progression**

Hr-QoL was assessed by the MSA-QoL questionnaire, developed in 2008.\textsuperscript{6} 11 The MSA-QoL is composed of 40 ordinal items (figure 1), each with five increasing levels of impairment (0 no, 1 slight, 2 moderate, 3 marked and 4 extreme impairment). The scale assesses three QoL domains: motor, non-motor and emotional/social. The original version was translated to adapt to the French-speaking audience.\textsuperscript{13} Since 2008, patients have been asked to complete the MSA-QoL questionnaire during each annual consultation.

**Ascertainment of MSA progression**

MSA progression was assessed at each visit by the Unified MSA Rating Scale (UMSARS)\textsuperscript{16} part IV, a score that ranks global disability in five stages (completely independent (stage I), needs help with some chores (stage II), needs help with half of the chores (stage III), does a few chores alone (stage IV) and totally dependent (stage V)).\textsuperscript{5, 6}

**Ascertainment of death and dropout**

At the time of administrative censoring, patients were either classified as deceased, still alive in the cohort or dropped out if their last visit was prior to 1 July 2020 (ie, more than 1.5 years before administrative censoring).

**Ascertainment of associated factors**

We considered the following factors that may influence Hr-QoL or personal perceptions: sex, age at inclusion, delay between symptom onset and inclusion, predominant syndrome (parkinsonian or cerebellar),\textsuperscript{10} diagnosis certainty (possible or probable), and presence of orthostatic hypotension (decrease greater than 10 mm Hg in diastolic or greater than 20 mm Hg in systolic blood pressure between the supine and upright positions) or urinary disorder (UMSARS-I item 10 score \(>2\)) at inclusion.\textsuperscript{5, 6} Treatment effects on Hr-QoL were explored for L-dopa (motor dimension), antihypotensive agents (non-motor) and antidepres-sants (emotional/social).

**Sample selection**

We included all patients who had completed at least one MSA-QoL questionnaire before administrative censoring and without missing data for all factors listed previously (online supplemental figure 1).

**Statistical analyses**

The longitudinal statistical analysis of Hr-QoL was divided into four steps to successively (1) identify the homogeneous dimensions within the scale, (2) model each dimension’s trajectory and explore disparities between patient profiles, (3) map items’ impairment hierarchy with the course of the disease and (4) identify the most informative items at each disease stage. Steps are briefly described below (see online supplemental appendix 1 for details).

**Step 1: identification of homogeneous subdimensions of MSA-QoL**

The different independent dimensions measured by the scale were identified using factorial analyses, following the Patient-Reported Outcomes Measurement Information System (PROMIS) methodology.\textsuperscript{17} The objective was to ensure that all items from a subdimension studied in steps 2-4 measured the same phenomenon (unidimensionality), did not carry redundant information (conditional independence) and higher levels of items always corresponded to higher levels of QoL impairment (increasing monotonicity). This step, necessary to ensure the validity of the statistical analyses in the subsequent steps, was carried out on all observed repeated individual follow-up data, representing 1537 MSA-QoL questionnaires for 557 patients.

Steps 2-4 were performed separately on each dimension. All patients with at least one item completed per (modified) dimension were included, leading to a sample of 536 patients with 1501 visits for step 2, and with at least 75% of the MSA-QoL items completed per (modified) dimension, leading to a sample of 516 patients with 1376 visits for step 3.

**Step 2: description of MSA-QoL item trajectories over time and their associated factors**

The trajectory of each dimension continuum was modelled over time using a longitudinal item response theory (lontgIRT) model for repeated graded item responses.\textsuperscript{18} 19 This model combined a linear mixed model to describe the underlying dimension deterioration over time according to covariates with cumulative probit measurement models to define the link between the underlying dimension and each item observation. To account for the informative truncation of QoL data induced by early deaths, the instantaneous risk of death was simultaneously modelled according to the dimension dynamics within a joint model.\textsuperscript{13} Dropouts were assumed missing at random. This assumption was checked in a sensitivity analysis by considering dropout as an informative event in competition with death. The linear mixed model included a linear function of time since inclusion at the population and individual levels and was adjusted for covariates as simple effects to explore phenotype differences according to sex, predominant syndrome, diagnosis certainty, age at inclusion, presence of orthostatic hypotension or urinary disorder at inclusion, delay since symptom onset and treatments. Time-dependent binary treatments were considered for the associated dimensions.

**Step 3: mapping of item impairment hierarchy to disease stages**

The sequence of item impairments derived from step 2 was defined according to the dimension-specific continuum and
Figure 1  Original and modified versions of the MSA-QoL questionnaire. The central part of the table lists the 40 items evaluating the health-related quality of life QoL in MSA. The left part of the table presents the allocation of items according to the original scale with three subdimensions: motor (14 items), non-motor (12 items), and emotional/social (14 items). The right part of the table presents the allocation of items according to the modified scale using PROMIS method with four subdimensions identified (and item 25 deleted): motor (11 items), oropharyngeal (4 items), non-motor (10 items), and emotional/social (14 items). MSA, multiple system atrophy, PROMIS, Patient-Reported Outcomes Measurement Information System, QoL, quality of life.

<table>
<thead>
<tr>
<th>Item</th>
<th>Original MSA-QoL questionnaire</th>
<th>PROMIS-modified MSA-QoL questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Had difficulty moving?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>2. Had difficulty walking?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>3. Had problems with your balance?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>4. Had difficulty standing up without support?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>5. Had difficulty speaking?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>6. Had difficulty swallowing food?</td>
<td>Oropharyngeal</td>
<td>Oropharyngeal</td>
</tr>
<tr>
<td>7. Had too much saliva or drooling?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>8. Had difficulty with handwriting?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>10. Had difficulty drinking fluids?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>11. Had difficulty dressing yourself?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>12. Needed help to go to the toilet?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>13. Had to stop doing things that you liked to do, e.g. your hobbies?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>14. Had difficulty doing things around the house, e.g. housework?</td>
<td>Motor</td>
<td>Motor</td>
</tr>
<tr>
<td>15. Experienced bladder problems?</td>
<td>Non-motor</td>
<td>X</td>
</tr>
<tr>
<td>16. Experienced problems with constipation?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>17. Experienced dizziness when standing up?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>18. Suffered from cold hands or feet?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>19. Experienced pain in your neck or shoulders?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>20. Experienced pain elsewhere, e.g. in your legs or your back?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>21. Had difficulty getting comfortable during the night?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>22. Had difficulty breathing during the night?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>23. Been feeling tired very quickly (without exerting yourself)?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>24. Experienced lack of energy?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>25. Experienced slowness of thinking?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>26. Had difficulty with your concentration, e.g. reading or watching TV?</td>
<td>Non-motor</td>
<td>Non-motor</td>
</tr>
<tr>
<td>27. Felt frustrated?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>28. Felt depressed?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>29. Experienced a loss of motivation?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>30. Been feeling incapable?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>31. Worried about the future?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>32. Worried about your family?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>33. Felt on your own or isolated?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>34. Experienced loss of confidence when interacting with others?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>35. Felt that your role in your family or among friends has changed?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>36. Experienced difficulty seeing your friends?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>37. Had to give up social activities, e.g. going out for a meal, participating in events?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>38. Had difficulty talking to friends about your illness?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>39. Been embarrassed to talk to people?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
<tr>
<td>40. Felt that life has become boring?</td>
<td>Emotional/social</td>
<td>Emotional/social</td>
</tr>
</tbody>
</table>
could not be overlaid across scale subdimensions. Step 3 consisted of anchoring each dimension continuum to the disease stage to improve the understanding of the sequences. This was achieved by jointly modelling the repeated data of a subdimension sum score with the repeated data of the disease stage (in a LongITRT model) and determining the level of each dimension continuum that corresponded to a change in disease stage.

Step 4: Listing of the most informative items by disease stage
Items do not necessarily contribute uniformly within and across disease stages. The contribution of each item was quantified through the percentage of information it carried at each stage (ie, the Fisher information the item carried standardised by the total Fisher information for a given disease stage).20 21 The most informative items were identified as those carrying the highest percentages of information at several disease stages.

RESULTS
Demographics
Among the 536 patients, 50% were women, 57.5% were from Bordeaux, 67.7% were diagnosed with MSA-P (MSA with predominant parkinsonism) and 74.6% with probable certainty (Table 1). Patients were on average 60.6 years old at symptom onset and 65.1 years old at inclusion, with a delay since symptom onset of approximately 4.5 years. At inclusion, 67.4% of patients had orthostatic hypotension and 68.1% had a urinary disorder. At inclusion, 68.3% were taking L-dopa, 30.0% antihypotensive agents and 20.7% antidepressants. A total of 1501 follow-up visits were analysed, representing approximately 2.8 observations per patient for a follow-up of 2.3 years (range=0–10.8 years). During follow-up, we recorded 63.1% deaths (mean follow-up 2.2 years, range=0–10.3) and 16.2% dropouts (mean follow-up 2.3 years, range=0–10.8); 20.7% were still alive in the cohort at administrative censoring (mean follow-up 2.6 years, range=0–8.5).

Identification of four MSA-QoL subdimensions
The PROMIS methodology confirmed the three dimensions previously identified by Schrag et al11 (figure 1) with motor, non-motor and emotional aspects, but it also isolated a fourth dimension featuring oropharyngeal impairment as assessed by items 6, 7, 9 and 10 from the original motor dimension. The distribution of the other items within each dimension was identical to the original distribution, except for item 15 (bladder problems) which was much more correlated with the motor items than the non-motor items and thus moved from the original non-motor dimension to the modified motor dimension. Items 25 (slowness of thinking) and 26 (difficulties concentrating) were strongly correlated providing redundant information. We thus removed item 25 from the modified scale. In the end, the modified MSA-QoL scale assessed four QoL dimensions: motor (10 items), oropharyngeal (4 items), non-motor (11 items) and emotional/social (14 items).

Table 1 Description of the MSA sample at inclusion and over time (N=536)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>268 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>268 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Centre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bordeaux</td>
<td>308 (57.5)</td>
<td></td>
</tr>
<tr>
<td>Toulouse</td>
<td>228 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Age at first symptom onset</td>
<td>60.6±8.1</td>
<td></td>
</tr>
<tr>
<td>Age at cohort entry</td>
<td>65.1±8.0</td>
<td></td>
</tr>
<tr>
<td>Years since first symptom onset</td>
<td>4.5±2.4</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSA-C, with predominant cerebellar impairment</td>
<td>173 (32.3)</td>
<td></td>
</tr>
<tr>
<td>MSA-P, with predominant parkinsonism</td>
<td>363 (67.7)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis certainty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>136 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Probable</td>
<td>400 (74.6)</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>361 (67.4)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>175 (32.6)</td>
<td></td>
</tr>
<tr>
<td>Urinary disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>365 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>171 (31.9)</td>
<td></td>
</tr>
<tr>
<td>Treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-dopa</td>
<td>366 (68.3)</td>
<td></td>
</tr>
<tr>
<td>Antihypotensive treatment</td>
<td>161 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>111 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Original MSA-QoL scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum score for motor dimension/56 (n=330)</td>
<td>27.0±12.2</td>
<td></td>
</tr>
<tr>
<td>Sum score for non-motor dimension/48 (n=344)</td>
<td>20.1±8.9</td>
<td></td>
</tr>
<tr>
<td>Sum score for emotional/social dimension/56 (n=326)</td>
<td>25.6±13.0</td>
<td></td>
</tr>
<tr>
<td>Modified MSA-QoL scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sum score for motor dimension/44 (n=333)</td>
<td>25.1±9.8</td>
<td></td>
</tr>
<tr>
<td>Sum score for oropharyngeal dimension/16 (n=387)</td>
<td>4.3±3.8</td>
<td></td>
</tr>
<tr>
<td>Sum score for non-motor dimension/40 (n=350)</td>
<td>16.6±7.8</td>
<td></td>
</tr>
<tr>
<td>Sum score for emotional/social dimension/56 (n=326)</td>
<td>25.6±13.0</td>
<td></td>
</tr>
<tr>
<td>Disability degree (n=520)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completely independent (stage I)</td>
<td>111 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Not completely independent (stage II)</td>
<td>239 (44.6)</td>
<td></td>
</tr>
<tr>
<td>More dependent (stage III)</td>
<td>105 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Very dependent (stage IV)</td>
<td>63 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Totally dependent (stage V)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>During follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visits</td>
<td>1501</td>
<td></td>
</tr>
<tr>
<td>Visits per patient</td>
<td>2.8±1.9</td>
<td></td>
</tr>
<tr>
<td>Years of follow-up</td>
<td>2.3±2.1</td>
<td></td>
</tr>
<tr>
<td>Early dropout</td>
<td>87 (16.2)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>338 (63.1)</td>
<td></td>
</tr>
</tbody>
</table>

MSA, multiple system atrophy; QoL, quality of life.
Drooling was reported to rapidly increase. In comparison, the non-motor and emotional spheres deteriorated very slowly. The most impacted items (with a roughly moderate impairment at entry) were lack of energy, fatigue and constipation in the motor dimension, since all items had already reached the maximum level at the beginning of stage V (figure 2). The degradation of non-motor and emotional/social dimensions was more progressive, occurring over the course of the disease.

Mapping QoL deterioration to disease stages (UMSARS-IV)

Projections of MSA disease stages onto the sequence of MSA-QoL impairments (figure 2) showed that motor and oropharyngeal dimensions were not affected during stage I but deteriorated very quickly over the subsequent stages with all their items reaching the maximum level by the beginning of stage V. The degradation of non-motor and emotional/social dimensions was more progressive, occurring over the course of the disease.

Most informative items over the disease course

The percentage of information carried by each item within the five MSA disease stages (figure 3 and online supplemental table 1) allowed the identification of the most informative items during the course of the disease.

In the motor dimension, since all items had already reached the maximum level at the beginning of stage V (figure 2), the most contributing items were identified from the four first stages only. They were as follows: 1 (moving), 2 (walking), 4 (standing up), 11 (dressing), 12 (toilet) and 14 (housework). Item 12, toilet, was poorly informative during stage I but captured an increasing proportion of information during stages II–IV (9%, 14% and 17%, respectively), as well as item 4, standing up, and item 11, dressing.

In the oropharyngeal dimension, item 7, saliva, carried 58% of the information at stage I but became secondary at later stages. At stages II–V, items 6 (swallowing), 9 (feeding) and 10 (drinking) became major providing together more than 85% of stage-specific information.

In the non-motor dimension, items 23 (tired) and 24 (energy) together carried more than 51%, 36%, 35% and 33% of the information for stages I, II, III and IV, respectively. Items 19 (neck/shoulder pain), 20 (leg/back pain) and 21 (comfortable) carried a large part of the information for stages II–V (more than 36%). In contrast, items 17 (dizziness), 18 (cold hands/feet), 22 (breathing) and 26 (concentration) were less relevant in the early disease stages.
Finally, in the emotional/social dimension, the information was more equally spread across items: no item seemed to concentrate all emotional Hr-QoL information regardless of stage. The four main items, 27 (being frustrated), 28 (depressed), 29 (loss of motivation) and 40 (feeling bored), carried slightly more information than the others over all stages (with more than 8% of information each at stages II, III and IV).

DISCUSSION

By leveraging Hr-QoL data from the French MSA cohort, we proposed a patient perspective on disease progression to improve MSA management. First, although not the primary objective of this work, the required preliminary evaluation of the MSA-QoL structure confirmed the original scale structure and isolated a fourth subdimension from the motor items focusing on oropharyngeal sphere. This additional subdimension is particularly significant, as feeding aspects are strongly impacted by MSA progression, with swallowing disorders being a major risk of death. Additionally, the factorial analyses led to the reclassification of bladder dysfunction (item 15) into the motor dimension. Although bladder disorder is a non-motor symptom, linked to the patients' inability to move to the toilet. Second, the dimensions exhibited distinct patterns of deterioration throughout the disease course. The motor and oropharyngeal dimensions showed minimal impairment during stage I but deteriorated rapidly thereafter. In contrast, the non-motor and emotional/social dimensions were slightly to moderately impaired at stage I and slowly progressive. Third, Hr-QoL impairments varied across patient profiles. Female patients experienced poorer overall Hr-QoL than males. Patients with MSA-P showed lower motor deterioration but higher oropharyngeal, non-motor and emotional/social deterioration than patients with MSA-C. These findings align with Xiao et al’s study. The presence of urinary disorders at inclusion and the delay since symptom onset influenced impairment, emphasising the need for early diagnosis. Patients receiving L-dopa and antihypotensive treatment exhibited higher Hr-QoL impairments in the motor and non-motor dimensions, respectively, suggesting either their limited effectiveness on QoL-related symptoms or their systematic prescription to the most affected patients.

This study identified the most informative Hr-QoL items, providing guidance to clinicians regarding the most critical domains. This information could facilitate personalised clinical attention and management. Throughout disease progression, key features emerge. In stage I, a more precise evaluation and treatment of drooling, particularly for patients with MSA-P, appeared beneficial. Additionally, early evaluation and treatment of urinary dysfunction were associated with better Hr-QoL. In stages II and III, the impact on activities of daily living and self-care, combined with increased loss of mobility, substantially contributes to QoL. Prioritising the implementation of technical and human assistance along with sustained rehabilitation to maintain autonomy appears crucial. Fatigue remained a key element throughout all stages of the disease. As reported in other studies, potential determinants such as orthostatic hypotension, sleep disorders or depressive symptoms can contribute to the fatigue reported by patients. Although orthostatic hypotension was not a major predictor, antihypotensive treatment was significantly associated with a higher impact of non-motor symptoms, such as fatigue and loss of energy. While the impact of sleep disorders was not evaluated, they are a common occurrence in MSA and may contribute to fatigue. Additionally, throughout the entire disease course, psychological support, with or without antidepressant treatment, appears crucial with early attention to self-esteem and future outlook, followed by consideration of the disease’s impact on social and family interactions. All recommendations to enhance the management of Hr-QoL in MSA are summarised in a mind map (figure 4).

The strengths of this study lie in the use of one of the largest MSA cohorts worldwide, with extensive duration of follow-up and high-quality data combined with an original statistical strategy. The cohort is still open and thus comprises patients included between 2007 and 2021 with follow-ups, thus varying from 0 to 11 years. The four-step statistical strategy addressed the challenges posed by repeated Hr-QoL data by decomposing the scale into independent subdimensions before the application of IRT-based modelling, accounting for the informative higher risk of death during the follow-up when describing each dimension’s trajectory, mapping the impairment hierarchy of Hr-QoL items with disease stages and identifying the most informative items.

This study also has limitations. First, it focused on HR-QoL progression as measured in the MSA-QoL scale, specifically developed and validated for MSA. It may have restricted the spectrum of HR-QoL aspects. Notably, dysautonomic features are under-represented or not directly measured within the scale. Dysautonomia may be reflected by items such as fatigue (23) and energy (24) that cover multiple symptoms, including orthostatic hypotension. Second, we investigated in step 2 a subset of all potential determinants of the dimensions’ progression. In particular, we only considered the main treatments (L-dopa, antihypotensive, antidepressant). We leave for future work the assessment of the role of other determinants, in particular other treatments. Although comprising very rich and standardised information regarding the MSA progression, the cohort contains little information around the onset and the end of the disease. Given the complexity of MSA diagnosis in early disease stages, patients may be included years after their first symptoms and with some heterogeneity across patients. This was accounted for by adjusting the progression on the delay since the first
symptoms. We only observed a small proportion of final stage V, and results specific to this stage should be interpreted with caution. As patients become severely disabled, they may die or refuse to participate anymore, thus truncating the HR-QoL data. In the main analyses, dropout was considered as predictable from the observed MSA-QoL items. However, we confirmed that the results were virtually the same when assuming the risk of dropout could be a competing informative event along with death (results not shown). Finally, although this study suggests a possible reclassification of some MSA-QoL items, and the identification of most informative items provides new avenues to monitor patients, this study does not call for a revision of the scale. Further dedicated analyses and replication on other MSA cohorts would be necessary to confirm the findings.

In conclusion, describing the natural history of HR-QoL in MSA through an innovative statistical approach provided practical recommendations for the management of patients with MSA. The same methodology could be replicated in other neurodegenerative diseases to improve disease understanding and management from the patient’s perspective.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Anonymised data can only be shared by reasonable motivated request to the MSA reference centre coordination. Anonymised data can only be shared by reasonable motivated request to the MSA French MSA Association ARAMISE, the MSA coalition, Lundbeck, ONO Pharma, Servier and Takeda. AF-S received honoraria from Agutattor Laboratory.

Author affiliations
1 Bordeaux Population Health Research Center, Inserm U1219, University of Bordeaux, Bordeaux, France
2 MSA French Reference Center, University Hospital Toulouse, Toulouse, France
3 Departments of Clinical Pharmacology and Neurosciences, University of Toulouse, CIC-1436, NeuroToul COEN Center, NS-Park/FCRIN Network, Toulouse University Hospital, Inserm U1048/1214, Toulouse, France
4 CIC1401-EC, Inserm, Bordeaux, France
5 CHU Bordeaux, Service de Neurologie des Maladies Neurodégénératives, IMIC, CRMR AMS, NS-Park/FCRIN Network, University of Bordeaux, CNRS, IMIC, UMR5293, Bordeaux, France
6 Department of Medicine, University of Otago, New Zealand Brain Research Institute, Christchurch, New Zealand

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ORCID iDs Tiphaine Saulnier http://orcid.org/0000-0001-8551-4200
Anne Pavy-Le Traon http://orcid.org/0000-0002-9375-1553

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**Figure S1: Flowchart of MSA sample selection.**
Patients without any completed MSA-QoL questionnaire, with missing values for at least one covariate of interest (among sex, age, subtype, diagnosis certainty, presence or absence of orthostatic hypotension at inclusion, presence or absence of urinary disorder at inclusion, delay since symptom onset, and treatments), and without at least one item completed per (modified) dimension were excluded from the analyses.

[Diagram showing the sample selection process]

**Footnote:** STEP 1 corresponds to the identification of the scale subdimensions; STEP 2 corresponds to the description of each subdimension trajectory over time; STEP 3 corresponds to the mapping of subdimension items with the disease stages.
Figure S2: Mean trajectories of Hr-QoL items over time predicted by a joint longitudinal IRT model for each modified-dimension.

Trajectories are represented for the reference profile: a male patient, diagnosed with probable MSA-P, aged 65 years old at inclusion, with orthostatic hypotension at inclusion but without urinary disorder at inclusion, with no delay since symptom onset and not receiving L-dopa, antihypotensive agents or antidepressants.
Appendix 1: Further details on the four steps constituting the MSA-QoL analysis strategy

Statistical analyses were carried out in R. A replication script is available at https://github.com/TiphaineSAULNIER/4StepStrategy.

1. Step 1: Identification of homogeneous MSA-QoL subscale dimensions

The different MSA-QoL dimensions measured by the scale were distinguished using the PROMIS methodology, ensuring the validity of the three calibration assumptions of the items: unidimensionality, conditional independence, and increasing monotonicity. This method permitted us to successively evaluate these assumptions. However, the authors recommended some stepbacks to measure the impact of certain decisions and to ensure that the identified dimensions made clinical sense. The methods used did not handle repeated data, so we performed the first step on all follow-up data by neglecting the intrasubject correlation.

First, an explanatory factorial analysis (EFA) was performed on all items to identify the different phenomena measured by the questionnaire. The optimal number of dimensions was determined according to the scree plot of the successive eigenvalues and based on the greatest number of factors with successive eigenvalues greater than 1 or the Kaiser criterion. This analysis was carried out using the function fa.parallel() from the R package psych. Then, each item was assigned to the dimension to which it most contributed, according to the polychoric correlation matrix. Afterwards, to confirm the result and to ensure the sufficient unidimensionality of the identified dimensions (i.e., all items from a dimension measure the same phenomenon), an EFA was performed for each dimension to control that the number of underlying factors was 1, and a confirmatory factorial analysis (CFA) was performed to evaluate the model fit based on PROMIS-recommended criteria thresholds: comparative fit index (CFI) > 0.95, Tucker Lewis index (TLI) > 0.95, root mean square error of approximation (RMSEA) < 0.06, and standardized root mean square residual (SRMR) < 0.08. This analysis was performed using the function cfa() from the R package lavaan.

To ensure conditional independence (i.e., items from the same dimension do not carry redundant information), the residual correlation matrix between the CFA-fitted values and the observed values of the items for each dimension was computed. According to PROMIS, the assumption is not satisfied for a residual correlation greater than 0.2 between two items, and in this case, removing one item is recommended.
To ensure increasing monotonicity (i.e., higher levels of items always correspond to higher levels of QoL impairment), a nonparametric IRT model was performed for each dimension using the function `check.monotonicity()` from the R package `mokken`. For each item, it computes the probabilities of endorsing a higher level and predicts the item level to be compared to the increasing dimension sum scores (except for the considered item score) through plots. According to the authors, the item response curves should be increasing or at least constant.

At this stage, each homogenous subscale was identified and analysed separately in Steps 2 to 4.

2. Step 2: Description of MSA-QoL item trajectories over time and associated factors

The trajectory of each dimension continuum was modelled over time from the repeated item data using a joint item response theory (IRT) model adapted to ordinal repeated measures and time-to-event data. The model, described in Figure S1, was simultaneously composed of a longitudinal submodel and a survival submodel, estimated by maximum likelihood in the R package JLPM (https://github.com/VivianePhilipps/JLPM). The longitudinal submodel combined the following:

(i) a linear mixed structural model to describe the underlying dimension deterioration over time according to covariates and functions of time, with the fixed effects defining the mean dimension trajectory at the population level and individual correlated random effects capturing individual deviations, and

(ii) an item-specific cumulative probit measurement model to define the link between the underlying dimension and each item observation.

The survival submodel was a proportional hazard survival model adjusted using the underlying dimension dynamics as a linear predictor to account for the informative dropout induced by deaths. For further details, please refer to Saulnier et al.
3. Step 3: Mapping item impairment hierarchy to disease stages

The disease stages were projected on a dimension continuum using a joint bivariate model to link the disease stages to the dimension total sum score. This was performed using the R package JLPM, which was also adapted for continuous markers by replacing the cumulative probit measurement model with linear and curvilinear measurement models (the curvilinear model involves a parameterized bijective link function approximated by splines). Then, thresholds in the dimension continuum corresponding to each disease stage were deduced by predicting the dimension sum scores that corresponded to a change in disease stage and expressing them in the dimension process scale. As this part requires the computation of dimension sum scores, it does not handle missing data. To limit the number of excluded data, dimension sum scores were computed in proportion to the number of missing items, as long as there were less than 25% missing item values. This optimal threshold was chosen as a balance between a maximal number of observations and a minimal proportion of missing items.

4. Step 4: Listing the most informative items by disease stage

The contribution of each item was quantified by the percentage of the carried information at each stage. The information was defined by the Fisher information function (i.e., the second derivative of the item probability with respect to the underlying dimension), which was integrated over all the underlying dimension values corresponding to a specific stage (as determined in Step 3) to obtain the item- and stage-specific information. The total information of a dimension at a specific stage was the sum of all item- and stage-specific
information so that the percentage of total information carried by an item at a disease stage was easily deduced.

References


Table S1: Ranking of MSA-QoL items per dimension for the 5 UMSARS-IV stages according to the item-specific Fisher information carried

<table>
<thead>
<tr>
<th>Rank</th>
<th>Item</th>
<th>Stage I</th>
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**MOTOR dimension**

1. Weak
2. Walking
3. Housework
4. Handwriting
5. Slurred speech
6. Incontinence
7. Speech
8. Dress
9. Stand up
10. Kneel
11. Toilet
12. Saliva
13. Drink
14. Feed
15. Visiting
16. Cognitive
17. Depression
18. Anxiety
19. Fatigue
20. Sleep
21. Memory
22. Breath
23. Energy
24. Mood
25. Neck/Shoulders pain
26. Back pain
27. Upper limb pain
28. Lower limb pain
29. Gastrointestinal symptoms
30. Renal symptoms
31. Sexual dysfunction
32. Respiratory symptoms
33. Psychological symptoms
34. Social activity
35. Family
36. Frustration
37. Sleep
38. Tiredness
39. Talk
40. Talk to
41. Solitude
42. Confidence
43. Friends
44. Talk to
45. Social activity
46. Communication
47. Self-esteem
48. Social isolation
49. Depression
50. Anxiety

**OROPHARYNGEAL dimension**

1. Saliva
2. Drink
3. Feed
4. Visiting
5. Cognitive
6. Depression
7. Anxiety
8. Fatigue
9. Sleep
10. Energy
11. Mood
12. Neck/Shoulders pain
13. Back pain
14. Upper limb pain
15. Lower limb pain
16. Gastrointestinal symptoms
17. Renal symptoms
18. Sexual dysfunction
19. Respiratory symptoms
20. Psychological symptoms
21. Social activity
22. Family
23. Frustration
24. Sleep
25. Tiredness
26. Talk
27. Talk to
28. Solitude
29. Confidence
30. Friends
31. Talk to
32. Social activity
33. Communication
34. Self-esteem
35. Social isolation
36. Depression
37. Anxiety

**NONMOTOR dimension**

1. Energy
2. Mood
3. Neck/Shoulders pain
4. Back pain
5. Upper limb pain
6. Lower limb pain
7. Gastrointestinal symptoms
8. Renal symptoms
9. Sexual dysfunction
10. Respiratory symptoms
11. Psychological symptoms
12. Social activity
13. Family
14. Frustration
15. Sleep
16. Tiredness
17. Talk
18. Solitude
19. Confidence
20. Friends
21. Talk to
22. Social activity
23. Communication
24. Self-esteem
25. Social isolation
26. Depression
27. Anxiety

**EMOTIONAL/SOCIAL dimension**

1. Incapacity
2. Future
3. Motivation
4. Role
5. Energy
6. Social activities
7. Family
8. Frustration
9. Sleep
10. Communication
11. Confidence
12. Friends
13. Talk
14. Solitude

Info %: percentage of Fisher information carried by the item.
Cum Info %: cumulative percentage of Fisher information carried by the item and the most informative ones.