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Original research

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

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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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although health-related quality of life (Hr-QoL) measures could provide crucial information on disease progression, they are insufficiently studied in neurodegenerative diseases. This work describes Hr-QoL progression during the disease natural course in more than 500 patients with multiple system atrophy.

WHAT THIS STUDY ADDS

⇒ The study answers how patients suffering from multiple system atrophy perceive the deterioration of their quality of life during disease course. The progression over time of quality of life dimensions was described along the clinical stages, and a mind map was built to help clinicians deliver better support.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Hr-QoL progression provides new perspectives on neurodegenerative diseases' management 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 affected[1–3] 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.[4–6] 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.[4 6 8 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 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

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patients with highest impairments.[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.[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[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.[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.[15] 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)[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)).[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),[14] 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.[5 6] Treatment effects on Hr-QoL were explored for L-dopa (motor dimension), antihypotensive agents (non-motor) and antidepressants (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.[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 (longIRT) model for repeated graded item responses.[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.[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

Original MSA-QoL questionnaire			PROMIS-modified MSA-QoL questionnaire
Motor	1. Had difficulty moving?		Motor
	2. Had difficulty walking?		
	3. Had problems with your balance?		
	4. Had difficulty standing up without support?		
	5. Had difficulty speaking?		
	6. Had difficulty swallowing food?		Oropharyngeal
	7. Had too much saliva or drooling?		
	8. Had difficulty with handwriting?		Motor
	9. Had difficulty feeding yourself?		Oropharyngeal
	10. Had difficulty drinking fluids?		
	11. Had difficulty dressing yourself?		Motor
	12. Needed help to go to the toilet?		
	13. Had to stop doing things that you liked to do, e.g. your hobbies?		
	14. Had difficulty doing things around the house, e.g. housework?		
Non-motor	15. Experienced bladder problems?		
	16. Experienced problems with constipation?		Non-motor
	17. Experienced dizziness when standing up?		
	18. Suffered from cold hands or feet?		
	19. Experienced pain in your neck or shoulders?		
	20. Experienced pain elsewhere, e.g. in your legs or your back?		
	21. Had difficulty getting comfortable during the night?		
	22. Had difficulty breathing during the night?		
	23. Been feeling tired very quickly (without exerting yourself)?		
	24. Experienced lack of energy?		
	25. Experienced slowness of thinking?		X
	26. Had difficulty with your concentration, e.g. reading or watching TV?		Non-motor
Emotional/social	27. Felt frustrated?		Emotional/social
	28. Felt depressed?		
	29. Experienced a loss of motivation?		
	30. Been feeling incapable?		
	31. Worried about the future?		
	32. Worried about your family?		
	33. Felt on your own or isolated?		
	34. Experienced loss of confidence when interacting with others?		
	35. Felt that your role in your family or among friends has changed?		
	36. Experienced difficulty seeing your friends?		
	37. Had to give up social activities, e.g. going out for a meal, participating in events?		
	38. Had difficulty talking to friends about your illness?		
	39. Been embarrassed to talk to people?		
	40. Felt that life has become boring?		

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 lifeQoL 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 atroph, PROMIS, Patient-Reported Outcomes Measurement Information System, QoL, quality of life.

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 longIRT 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).

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

Characteristic	N (%)	Mean±SD
At inclusion		
Sex		
Male	268 (50.0)	
Female	268 (50.0)	
Centre		
Bordeaux	308 (57.5)	
Toulouse	228 (42.5)	
Age at first symptom onset		60.6±8.1
Age at cohort entry		65.1±8.0
Years since first symptom onset		4.5±2.4
Diagnosis		
MSA-C, with predominant cerebellar impairment	173 (32.3)	
MSA-P, with predominant parkinsonism	363 (67.7)	
Diagnosis certainty		
Possible	136 (25.4)	
Probable	400 (74.6)	
Orthostatic hypotension		
Presence	361 (67.4)	
Absence	175 (32.6)	
Urinary disorder		
Presence	365 (68.1)	
Absence	171 (31.9)	
Treatments		
L-dopa	366 (68.3)	
Antihypotensive treatment	161 (30.0)	
Antidepressants	111 (20.7)	
Original MSA-QoL scale		
Sum score for motor dimension/56 (n=330)		27.0±12.2
Sum score for non-motor dimension/48 (n=344)		20.1±8.9
Sum score for emotional/social dimension/56 (n=326)		25.6±13.0
Modified MSA-QoL scale		
Sum score for motor dimension/44 (n=333)		25.1±9.8
Sum score for oropharyngeal dimension/16 (n=387)		4.3±3.8
Sum score for non-motor dimension/40 (n=350)		16.6±7.8
Sum score for emotional/social dimension/56 (n=326)		25.6±13.0
Disability degree (n=520)		
Completely independent (stage I)	111 (20.7)	
Not completely independent (stage II)	239 (44.6)	
More dependent (stage III)	105 (19.6)	
Very dependent (stage IV)	63 (11.8)	
Totally dependent (stage V)	2 (3.0)	
During follow-up		
Visits	1501	
Visits per patient		2.8±1.9
Years of follow-up		2.3±2.1
Early dropout	87 (16.2)	
Death	338 (63.1)	

MSA, multiple system atrophy; QoL, quality of life.

Identification of four MSA-QoL subdimensions

The PROMIS methodology confirmed the three dimensions previously identified by Schrag *et al*[11] (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).

Item trajectories and sequences and associated factors

Most of the items already showed partial impairment at inclusion for the reference patient profile (online supplemental figure 2), with the exception of the oropharyngeal items (swallowing, feeding and drinking). The items in the motor dimension deteriorated very rapidly over the first 4 years of follow-up, with most of the items reaching level 3 (marked impairment) less than 5 years after inclusion. Moving, walking, balance, housework and hobbies were already perceived as moderately impaired (level 2) at inclusion. Dressing and requiring help to go to the toilet were moderately impaired by 3–4 years after inclusion. The oropharyngeal items progressively deteriorated, reaching moderate impairment approximately 5 years after inclusion and marked impairment by 10 years in the reference patient category.

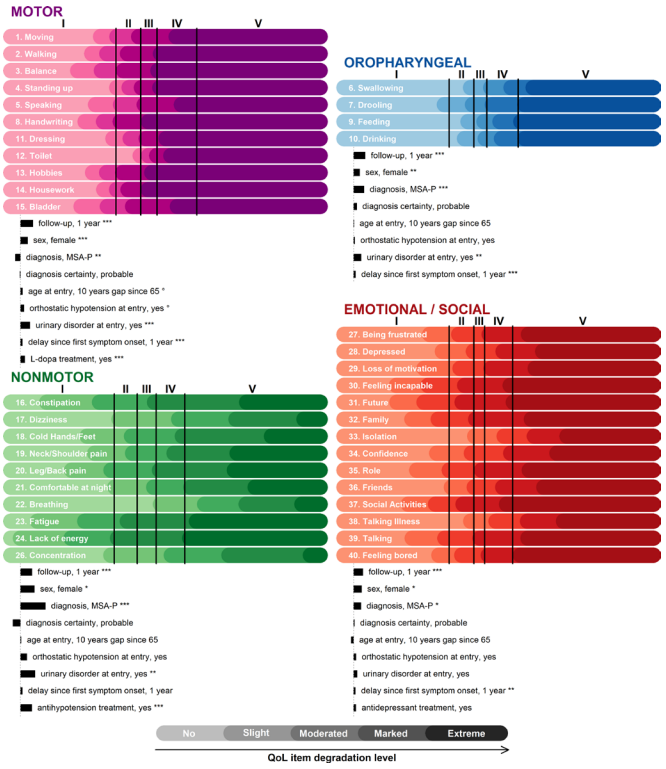

Figure 2 Sequence of Hr-QoL item impairment according to disease stage and associated factors for each subdimension. Each graph represents the items' degradation according to the underlying subdimension continuum. The colour gradient reflects increasing impairment, that is, the lightest colour for level 0 ('no problem') to the darkest colour for level 4 ('extreme problem'). The intensity of the change in the underlying continuum due to each factor is represented by the horizontal black bar. The significance of a covariate effect is denoted by '°' for p≤0.1, '*' for p≤0.05, '**' for p≤0.01 and '***' for p≤0.001 (very significant) with *p* the associated Wald test p value. The four vertical black lines indicate the estimated location of the five MSA disease stages on each subdimension continuum. The different reference categories are male, MSA-C subtype, diagnosis with possible certainty, no orthostatic hypotension or urinary disorder at entry, no delay since symptom onset and no treatment (among L-dopa, antihypotensive agents and antidepressants). Hr-QoL, health-related quality of life; MSA, multiple system atrophy; MSA-C, MSA with predominant cerebellar impairment; MSA-P, MSA with predominant parkinsonism.

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 non-motor dimension and participation in social activities and concerns about the future in the emotional/social dimension.

The sequence of the item impairments according to each subdimension continuum was derived from the model (figure 2). Within the motor dimension, balance (item 3), handwriting (8) and bladder (15) problems occurred first, followed by difficulties walking (2), speaking (5) and continuing hobbies (13). Difficulties going to the toilet arose later than other motor impairments but progressed rapidly. In the oropharyngeal dimension, drooling occurred first (7). In the non-motor dimension, fatigue (23), lack of energy (24) and constipation (16) occurred first, followed by localised pain (18, 19 and 20) and night discomfort (21). In the emotional/social dimension, patients first felt incapable (30), worried about their future (31) and their family (32), gave up social activities (37) and were embarrassed to talk to people (39). Then, they gradually lost their motivation (29), their confidence (34) and felt bored (40), frustrated (27) and depressed (28) to the point of breaking ties with their friends (36) and isolating (33).

Each subdimension continuum was modulated by other factors (figure 2). The motor and oropharyngeal dimensions deteriorated much more rapidly than the non-motor and emotional dimensions. Female patients had poorer Hr-QoL than males in the four dimensions. Patients diagnosed with MSA-P had significantly lower motor but higher oropharyngeal, non-motor and emotional/social deteriorations on average than patients diagnosed with MSA-C (MSA with predominant cerebellar impairment). In the non-motor dimension, the difference in impairment between patients with MSA-P and those with MSA-C was equivalent to the effect of 2 years of progression. There were no noticeable differences in diagnosis certainty, age or the presence of hypotension at inclusion. Patients suffering from urinary disorders at inclusion had a lower Hr-QoL according to the motor, oropharyngeal and non-motor dimensions. The delay since symptom onset was associated with higher Hr-QoL impairment in the motor, oropharyngeal and emotional/social dimensions. Finally, Hr-QoL impairment appeared higher in the motor dimension for patients taking L-dopa and in the non-motor dimension for patients under antihypotensive treatment.

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.

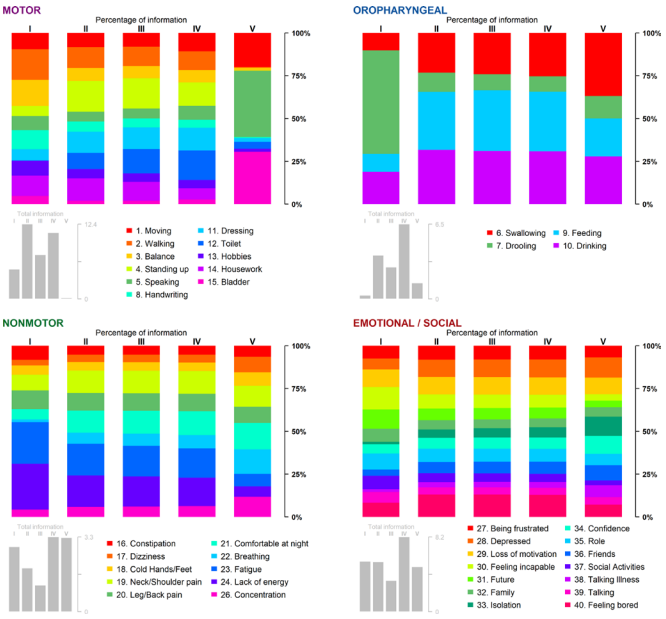

Figure 3 Item contribution for each subdimension across the five MSA disease stages. The larger the colour bar, the more the item contributed. Grey bar plots report the total information carried by the items for each subdimension to the five disease stages. MSA, multiple system atrophy.

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, the patient's perception of this item may involve substantial motor issues, 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[10] 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,[22] 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[23] 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.[11] 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

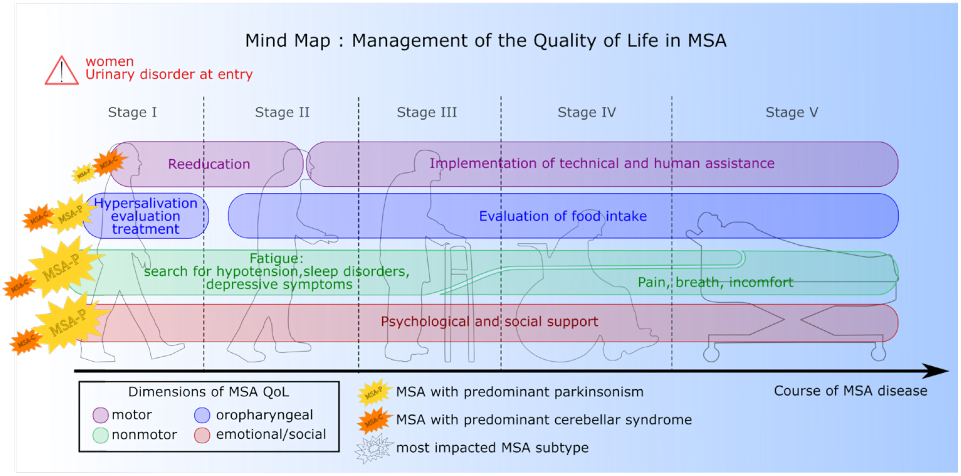

Figure 4 Pathway for improving Hr-QoL management in MSA. Hr-QoL, health-related quality of life; MSA, multiple system atrophy; MSA-C, MSA with predominant cerebellar impairment; MSA-P, MSA with predominant parkinsonism.

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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