A systematic review of the spectrum and prevalence of non-motor symptoms in multiple system atrophy

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Abstract

Background

Patients with Multiple System Atrophy (MSA) frequently report non-motor symptoms, and several research groups have highlighted this.

Objective

We systematically searched for and reviewed papers assessing prevalence of non-motor symptoms (NMS) in MSA patients as reported in the scientific literature.

Methods

We performed a systematic review of studies of subjects with MSA (involving >5 patients) who were assessed for NMS, published in the English literature in PUBMED and EMBASE databases from 1947-2022.

Results

23 research papers, with data from 2648 clinically diagnosed and 171 pathologically verified cases of MSA were included, along with 238 controls. Mean age for MSA cases was 61.3 (9.2) years, mean disease duration 3.6 (2.7) years. 57.9% were male. Our analysis showed that the prevalence of cognitive issues in MSA widely varied (between 15-100%); dementia per se was uncommon, but assessment in advanced stages is impacted by unintelligible speech (which may be noted in a quarter of cases). The prevalence of depressive symptoms in MSA was between 44-88% and sleep disturbances were reported among 17-89%, with REM-sleep behaviour disorder (RBD) rates as high as 75%. Pain was reported by 40-47% of patients: rheumatic or musculoskeletal sources of pain being commonest, and fatigue in 29-60%. Symptoms of autonomic failure in MSA were seen in 34-96.5% patients at baseline.

Conclusion

In routine clinical practice, NMS in MSA are under-recognised by clinicians. These impact hugely on patient quality of life and contribute to overall morbidity. The methodical ascertainment of these complaints will address an unmet need, and lead to better and more wider approach of care in individuals with MSA.

Introduction

Multiple system atrophy (MSA) is an alpha-synucleinopathy with prominent autonomic features, that presents either with a cerebellar syndrome (MSA-C) or Parkinsonism, with a poor response to levodopa (MSA-P). MSA patients usually present in the sixth decade of life, have a progressive illness, with a shortened life span (median survival of less than 10 years[1]). Patients present with a variety of non-motor symptoms (NMS) besides autonomic dysfunction, but the historical focus has always been on autonomic symptoms only, overshadowing other NMS. In fact there are case reports of pathologically proven MSA who presented with only NMS and no motor features of parkinsonism or a cerebellar syndrome [2]. The MSA clinical spectrum is wider than was originally thought, and can include various NMS at disease onset [3]. Constipation is by far the commonest autonomic system NMS and is more prevalent than urinary incontinence and orthostatic hypotension [1]. Other symptoms MSA patients frequently report are sexual dysfunction, symptoms of REM-sleep behaviour disorder (RBD), dysphagia, and snoring[4]. In order to evaluate the prevalence of all NMS in MSA including and beyond those related to

autonomic dysfunction, we conducted a systematic review to appraise recent literature regarding the nature and prevalence of all NMS in MSA. To our knowledge, there is no other systematic review that has been performed on this topic. This appears to be knowledge gap, with potential implications on the holistic management of patients with MSA.

Methods

We searched PUBMED and EMBASE databases for papers published between 01/01/1947 and 10/02/2022 using a multi-field search strategy (electronic search strategy algorithm shown at end of paper) using the "Knowledge Network NHS Scotland" search engine (which allows combinations of multiple medical subheadings (MeSH)). The MeSH term 'multiple system atrophy' was combined with the main categories of non-motor symptoms: i.e., 'multiple system atrophy' and either 'sleep'; 'depression'; 'anxiety'; 'pain'; 'cognition'; 'fatigue'; 'autonomic'. Two authors (CM, NM) conducted independent searches and a third author (RDS) resolved any discrepancies. Identified papers from these searches were then read in detail and summarised. Inclusion criteria required a case series with >10 patients with MSA and a detailed description of their NMS. Conference abstracts, book chapters, single case reports and review papers were excluded. Papers that did not include humans and were not published in the English language were excluded. The reporting of the electronic searches were conducted in line with the requirements of the PRISMA statement (Figure 1)[5]. Papers that provided only a statistical comparison of raw scores (between cases and controls) on scales, inventories or tests of cognition, mood, sleep or behaviour, without specifying what proportion of

their MSA cases had a particular NMS, and previously conducted meta-analyses by others were excluded from results tables, but were included in the discussion section.

Results

Our electronic search strategy identified 23 papers for MSA (both MSA-C and MSA-P) which met all inclusion and exclusion criteria. The results from our search strategy, detailing NMS in MSA (Figure 2, Tables 1a and 1b) grouped by major categories of NMS are shown.

Cognitive symptoms

Cognitive impairment is seen in both subtypes of MSA. Both MSA-P and MSA-C patients exhibit impaired executive and visuospatial functions, while attention deficit is predominant only in MSA-C [6]. While mild cognitive impairment is reported in a quarter of patients with MSA, the prevalence of dementia is much less[7]. Nevertheless the prevalence of dementia increases with disease duration and may be more common in females with MSA[7]. Dementia was evident in 14% of an MSA cohort (n=14) from Brazil, after an average disease duration of 3.5 years [6].

Anxiety, depression, and psychosis

Nearly half of the MSA patients enrolled in the European MSA study group (n=115) had moderate to severe depression[8]. In another study which evaluated the effects

of gender on cognitive and behavioural manifestations in MSA, the prevalence of apathy (55%) and depression (70%) was higher among female patients compared to males (40% versus 52% respectively).

Sleep disturbances

Sleep disturbances are commonly reported by MSA patients, with 87.2% prevalence rate in one study from China [9]. Night-time sleep disturbances in patients with MSA include RBD, restless legs syndrome (RLS) and periodic limb movements (PLM) in sleep[10]. All these symptoms lead to sleep fragmentation and decreased sleep efficiency[10]. Probable RBD, which is considered a red flag by the European MSA Study group [11], was reported in in 90.2% with possible MSA in a Korean cohort (n=61)[4].On the other hand in a European study (n=158), the prevalence of RBD symptoms was 76.6%, while RBD confirmed by video polysomnography was 67.7%[12].

Fatigue

Fatigue was reported in more than a quarter (28.7%) of patients from a cohort of 174 patients who met criteria for probable MSA. Results of multivariate analysis revealed that anxiety (OR = 3.01), excessive daytime sleepiness (OR = 2.70), and use of sleep medicine (OR = 3.58) were significantly associated with fatigue in MSA patients[13]. Another study conducted in China demonstrated a higher prevalence of fatigue: 60.3%, 55.1%, and 64.9% among those with MSA, MSA-P, and MSA-C, respectively[14]. This study showed that 48.6% (71/146) of patients had persistent

fatigue, 11.6% (17/146) had non-persistent fatigue, 15.1% (22/146) never had fatigue, while 24.7% (36/146) had new-onset fatigue. There were no significant difference in the patterns between the MSA-P and MSA-C subgroups[14].

Smell and taste disturbances

Disturbances in smell or taste have been reported among 23.3% of MSA patients in one study[15] which utilised the NMSS questionnaire. More specifically, olfactory loss or hyposmia have also been reported in nearly a third of patients with MSA[16].

Pain

Compared to healthy controls (n=40), those with MSA (n=65) have been found to have a significantly higher presence of pain ($p<0.01$)[17]. However, no difference in visual analog scores for pain were observed between PD (n=71) or MSA patients in this study ($p= 0.148$)[17]. Pain was reported in 39.5% of MSA patients in another large cohort of cases (n=172) from China[9]. Using the body pain section of the SF-36 questionnaire, in one study[6] MSA-P patients reported more severe pain (median score 51.5), compared to MSA-C (median score 20). Older reports have also documented high frequency of pain (47%) in MSA[18]. In a cohort of 100 consecutive patients with probable MSA (82 MSA-P, 18 MSA-C) the pain was classified as rheumatic in 64%, sensory in 28%, dystonic in 21%, and levodopa-related in 16% which were mostly related to off-period or diphasic dystonias[18]. There was a mixed pain syndrome in 19% of these patients[18]. Pain was significantly more commonly reported by females ($p=0.02$), and by patients with

levodopa-induced dyskinesias (p=0.02)[18]. The mean delay between disease onset and onset of pain was 2.9 years, but pain was reported at the time of or before disease onset in about 30% of patients [18].

Gastrointestinal symptoms

In a cohort of 172 patients with MSA (76 MSA-P, 96 MSA-C) gastrointestinal symptoms were reported by 72.7% [15]. In another study from China (n=143), swallowing and choking problems were reported by 50%, sialorrhea by 70%, dysphagia by 20%, constipation by 70%, straining for faecal defaecation by 70% and faecal incontinence by 10%[19]. The prevalence of dysphagia or the need for percutaneous gastrostomy tube feeding was much higher in those patients with MSA who has RBD symptoms (31%) compared to those without these symptoms (12%)(p=0.018)[12].

Cardiovascular symptoms

Neurogenic orthostatic hypotension is one of the hallmarks of MSA, but when treated patients may consequently suffer from supine hypertension. In one cohort of 14 patients with MSA (10 MSA-P, 4 MSA-C) postural hypotension was present in 57% of patients; while orthostatic symptoms such as mental confusion, dizziness, weakness, fatigue, nausea, palpitations, headache, or blurred vision on standing were present in 79% of MSA patients[6]. In a cohort of 172 patients with MSA (76 MSA-P, 96 MSA-C) from China, cardiovascular symptoms were reported by 70.9% [15]. A bigger European study (n=261) also reported a similar prevalence of

orthostatic hypotension (71%) at their first visit, which was slightly higher in MSA-P (72%) compared to MSA-C(68.5%) but this difference was not statistically significant (p=0.52)[20]. This study also reported the prevalence of supine hypertension at the first visit was 47.9%, although again there were no statistically significant differences between MSA-P and MSA-C subgroups(p=0.092)[20].

Urinary symptoms

In a large prospective natural history study of MSA, urinary symptoms (88%) (including urinary incontinence in 73% and incomplete bladder emptying in 51%) were more common than orthostatic hypotension (57%)[21]. In a cohort of 172 patients with MSA (76 MSA-P, 96 MSA-C) urinary problems were reported by 91.3%[15]. In another cohort of MSA patients from China (n=146), urinary incontinence was reported in 67.8% of patients at baseline with the prevalence increasing to 74% at 1 year follow-up[14].

Sexual dysfunction

Sexual dysfunction was reported in 95.1% patients with MSA[4]. In a cohort of 172 patients with MSA (76 MSA-P, 96 MSA-C) sexual problems were reported by 72.7%[15]. A history of erectile failure in men was present in 80% as the first autonomic symptom in another cohort of 158 patients with MSA (of which 79 MSA-P, 79 MSA-C; 63% male)[12].

Other autonomic symptoms

Symptoms of autonomic failure are present in nearly all patients with MSA (96%)[21]. The frequency of constipation (82.0%) and snoring (70.5%) was also high in MSA, even at early stages, with disease durations of 3 years or less[4]. In a cohort of 172 patients with MSA (76 MSA-P, 96 MSA-C) excessive sweating was reported in 26.2%[15].

Critical appraisal of studies included

We analysed the studies included in Tables 1a and 1b in detail to assess for threats to validity from risk of bias including selection, detection, analysis, attrition, and reporting biases. We graded these biases as low risk, high risk or not clear (Supplementary Table 1).

Discussion

While NMS are well-recognised as a clinical manifestation of Parkinson's disease (PD), they are not exclusively present in PD alone and have also been broadly described in other atypical Parkinsonian syndromes. The earliest symptoms of MSA are frequently autonomic and may often predate the motor symptoms, as is often the case in PD[22]. Orthostatic hypotension and erectile dysfunction in men are among the most prominent autonomic symptoms of MSA[22]. However, the true prevalence of autonomic symptoms in patients with MSA may be confounded or masked by concurrent medication use at the time of NMS assessment. For example, the use of blood pressure augmenting agents or those for bladder dysfunction may mask

features of autonomic failure among MSA patients[1].The first recalled symptom before a confirmed diagnosis of MSA is usually autonomic in three quarters of patients, but in about a fifth of cases it can be a sleep-related symptom[22].

Sleep disorders are even more prevalent in MSA than PD. 70% of patients with MSA patients in one study (n=57) complained of sleep disorders, compared with 51% of patients with PD (n=62)(p=0.03)[23]. The most commonly reported sleep disorders were sleep fragmentation (52.5%), vocalisation (60%), RBD (47.5%), and nocturnal stridor (19%)[23]. A previous meta-analysis reported an overall prevalence of clinically suspected RBD in 73% and polysomnography-confirmed RBD in 88% [24]. As a result of nocturnal sleep fragmentation, many patients exhibit resultant excessive day time sleepiness (EDS) the following day. Furthermore, the presence and severity of EDS is associated with other NMS including fatigue, anxiety, depression and cognitive dysfunction[25]. NMS, like depression, have a direct corelation with the health-related quality of life patients in MSA[8]; hence emphasising the importance of their identification and management.

Of more recent interest is cognitive dysfunction in MSA. While previously, dementia was indicated as an exclusionary diagnostic criterion for MSA, more recent studies with detailed neuropsychometric assessments have shown that clinically-defined dementia is present in 14-16% of cases[26]. About a third of cases of MSA show frontal dysfunction on the frontal assessment battery[27]. Cognitive dysfunction similarities between MSA and PD (both of which are alpha-synucleinopathies), suggest the role of basal ganglia dysfunction and corresponding frontal deafferentation in the occurrence of cognitive deficits[28].

It is interesting to note that there are gender differences in the prevalence of apathy, depression, and dementia in patients with MSA; all these symptoms have a higher prevalence in females compared to males with MSA[7].

Pain is very common in MSA, and affects nearly half of patients with MSA[18] and may even be pre-motor symptom[29]. However, in some cases pain symptoms may have a delayed onset by up to 4 years (range 0.5-21 years)[18]. The two most common pain locations in the MSA patients are in the back (36.7%) and neck/shoulder (23.3%)[17]. This latter type of pain location, referred to as coat-hanger pain was previously thought to be pathognomonic of MSA (related to more severe postural hypotension), but as evidenced in one study[30], this may be as common in PD as in MSA. Pain in MSA, as in PD, seems to improve with dopaminergic therapy in about half of cases[30], perhaps suggesting a central pathogenesis to pain symptoms. It can therefore be argued that optimizing dopaminergic treatments may equally as important in MSA in the management of pain symptoms, even if there is a poor response to the motor symptoms associated with the disease[30].

There are few longitudinal studies of NMS in MSA, with most studies cross-sectional in nature. However, one longitudinal study among MSA patients showed that most NMS, including urinary, sexual and sleep dysfunction, show a progression over time [31], while another study showed that autonomic dysfunction showed less sensitivity to change compared to motor symptoms[32]. Nevertheless, even in this study all NMSS sub-domain scores progressed over a 2-year follow-up period[32]. However, the clinical scales used for monitoring the progression of MSA, such as the unified

multiple system atrophy rating scale (USMARS)[33], are not sensitive enough for NMS evaluation in MSA[31] nor designed for the purpose of assessing NMS. The NMSS scale, validated for use in Parkinson's disease[34], has also been used in MSA[15] for lack of a better or a more suitable disease-specific scale. Such a scale for assessment of NMS in MSA will have to be based on an observational multicentre cross-sectional studies, requiring the enrolment of several hundred MSA patients in order to form a training cohort, with subsequent validation in other cohorts to test the scale's acceptability, reliability and internal consistency. In some studies, the Queen Square cardiovascular autonomic function test battery, the composite autonomic symptom scale (COMPASS) and measurements of residual urinary volume[35] have also been used in addition to the more traditional instruments (the Beck Depression Inventory and structured sleep questionnaires), as the USMARS Parts 1 and 3 can only capture a limited number of NMS[33].

As observed in previous studies, and much like other neurodegenerative diseases such as PD, MSA can also be characterised by prodromal stages wherein NMS may predominate development of the motor syndrome[22]. Identification of such a prodromal stages may arguably facilitate early therapeutic intervention in the future with disease modifying interventions when researchers have found good biomarkers of MSA, again emphasising the vital importance of early recognition of NMS during the prodromal stage of MSA.

Study Limitations

It was not possible to identify differential trends in the prevalence of NMS between the two subtypes MSA-P and MSA-C as only a handful of the papers included in this systematic review had dichotomised their cohorts into MSA-P and MSA-C but we have analysed this and the data are available for review upon request from the corresponding author of this systematic review. We cannot completely exclude bias in some of the studies due to undeclared conflicts of interests in the papers we have reviewed. The focus on one or more NMS in individual studies may reflect the research interests of the involved investigators, and their *a priori* hypotheses. Furthermore, due to the heterogeneity of the study populations and small numbers of patients in some studies, the generalisability of study findings may be limited.

Conclusion:

A comprehensive, symptom-based and validated questionnaire for NMS is needed, to ascertain the true spectrum and prevalence of NMS in patients with MSA. The recognition of the entire spectrum of NMS, not just limited to autonomic dysfunction in MSA, is required to enable the treating physicians to prescribe symptomatic treatments in a holistic and bespoke manner.

Figure and Table Legends

Figure 1. PRISMA diagram showing how the papers were included in this systematic review.

Figure 2: Prevalence of various non-motor symptoms in Multiple System Atrophy (coloured bars show the range of reported prevalence from the studies included in this systematic review.

Table 1a. Demographic details of cases with multiple system atrophy included in this systematic review

Table 1b. Prevalence of non-motor symptoms in cases with progressive cerebellar ataxia included in this systematic review. RBD= REM sleep behaviour disorder, EDS= excessive daytime sleepiness, RLS= Restless legs syndrome, † = orthostatic symptoms , ††= orthostatic hypotension, *= urinary incontinence

Supplementary Table 1: Critical appraisal of papers – Risk of bias analysis of papers included in this systematic review (papers listed according to year of publication.

Declarations :

Ethical approval :

The authors confirm that the approval of an institutional review board / patient consent was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Author roles:

C.M. Chulika Makawita, P.A. Piriyankan Ananthavarathan, RDS Rajith De Silva, N.M. Naveed Malek

1. Research Project: A. Conception, B. Organization, C. Execution;
2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique

C.M.: 1B, 1C, 2A, 2B

P.A.: 1B, 1C, 2A, 2B

RDS.: 1A, 1B, 2B

N.M.: 1A, 1B, 1C, 2A

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All authors report no conflicts of interest

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Availability of data and materials:

Data and materials are available up on request

Electronic search strategy:

1. (multiple system atrophy and sleep) or multiple system atrophy) and anxiety) or multiple system atrophy) and fatigue) or multiple system atrophy) and pain) or multiple system atrophy) and cognition) or multiple system atrophy) and autonomic) or multiple system atrophy) and depression).
2. limit 1 to English language
3. limit 2 to humans
4. Remove duplicates from 3

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