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Short communication

Pre-diagnostic presentations of Multiple System Atrophy case control study in a primary care dataset

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ABSTRACT

Background: We here report the pre-diagnostic clinical presentations of patients with Multiple System Atrophy (MSA) from analysis of a large routine clinical care database.
Methods: Data were extracted from a primary care database in the German healthcare system for the period between January 2000 and December 2020. We identified 250 patients with new diagnosis of MSA and 250 controls matched for age, sex, and index year. Logistic regression analyses were conducted to assess association between MSA and predefined diagnoses.
Results: The greatest rate increase in the 2 years preceding diagnosis of MSA was seen for hypotension and balance impairment but rates of memory problems, urinary dysfunction, dizziness and depression rates were also markedly increased, and ataxia was solely identified in those with a later diagnosis of MSA. Up to 5 years before diagnosis similar patterns were seen, but >5 years before diagnosis only depression rates were increased with a trend for increase in constipation.
Conclusions: Presentations that were significantly more common in patients with MSA in the pre-diagnostic phase than in controls were autonomic complaints such as postural hypotension, urinary and bowel dysfunction, and early balance impairment. However, the study also highlights that memory complaints and depression may be early features of MSA years before diagnosis.

1. Introduction

In Parkinson's disease, a pre-diagnostic phase of the disease is well established and includes a number of motor and non-motor features, predating the diagnosis often by several years. However, there is little information on the pre-diagnostic features of Multiple System Atrophy (MSA) [1], and reports on the development of initial features are primarily based on retrospective patient reports [2–4]. We here report the pre-diagnostic clinical presentations of patients with MSA from analysis of data from a large, representative database of routine care consultations in Germany.

2. Methods

2.1. Database

Data from the Disease Analyzer database (IQVIA) in Germany were used for this study. This database has been described previously [5]. Briefly, it contains demographic, diagnosis, and prescription data obtained in anonymized format from medical practices in Germany. Diagnoses are coded using the German adaptation of the International Classification of Diseases, 10th revision (ICD-10), and prescriptions are coded using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). The Disease Analyzer database covers approximately 3% of German medical practices. Previous research has shown that this database is representative of primary care practices in Germany(5).

2.2. Study population

This case control study included 9,856,800 patients aged ≥18 years from 1198 primary care practices between January 2000 and December 2020. Patients with an incident diagnosis of MSA were identified using ICD-10 codes G23.2 and G23.3. Controls without a diagnosis of MSA or

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PD (ICD-10: G20, G21) were randomly selected, matched by sex, age, and index year. In controls, the index date corresponded to a randomly selected visit date between January 2000 and December 2020. Patients with less than twelve months follow-up from registration prior to the index date were excluded, in order to avoid inclusion of patients with existing diagnoses of MSA (suppl. Figure 1).

2.3. Study outcomes

The occurrence of defined diagnoses and symptoms previously reported to be associated with later diagnosis of MSA were recorded. Three periods were analyzed: Within 0 to <2 years, ≥2 years to <5 years, and ≥5 years to <10 years prior to the index date.

The diagnoses analyzed included: tremor (ICD-10: R25.1), shoulder pain or stiffness (ICD-10: M25.5), neck pain or stiffness (ICD-10: M54.2), joint stiffness (ICD-10: M24.5, M24.6, M25.6), balance impairments (ICD-10: R26), depression (ICD-10: F32, F33), anxiety (ICD-10: F41), memory problems (ICD-10: F06.7, R41), insomnia (ICD-10: G47.0, G47.9), constipation (ICD-10: K59.0), urinary dysfunction (ICD-10: N39.3, N39.4, N39.9), erectile dysfunction (ICD-10: F52), hypotension (ICD-10: I95), dizziness (ICD-10: R42); fatigue (ICD-10: F32, G93.3, R53), sleep apnea (ICD-10: G47.3), Raynaud's syndrome (ICD-10: I73.0), restless legs syndrome (ICD-10: G25.8 plus original text of the physician), ataxia (ICD-10: R26.0, R27.0).

2.4. Statistical analyses

Baseline characteristics were compared between patients with MSA and controls using McNemar and Wilcoxon signed-rank tests. Logistic regression analyses were conducted to assess the association between MSA and the predefined diagnoses/symptoms. P-values lower than 0.05 were considered statistically significant. Analyses were conducted using SAS 9.4 (SAS institute, Cary USA).

Statement of ethics

The German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no institutional review board approval was required for the use of this database or the completion of this study.

3. Results

The study included 250 patients with MSA and 250 matched controls. Of these, 211 with MSA and 202 controls had been followed for at least 2 years before the index date, 148 with MSA and 137 controls had at least 5 years of follow-up, and 74 with and 69 without MSA had at least 10 years of follow-up data prior to the index date. The groups did not differ with regard to sex and age (Table 1).

Within two years prior to the index date, the strongest association with later diagnosis of MSA was observed for hypotension (OR = 15.69; 95% CI: 2.06–119.40), balance impairment (OR = 11.23; 95% CI: 3.38–37.29), memory problems (OR = 8.53; 95% CI: 1.07–67.92), and urinary dysfunction (OR = 4.49; 95% CI: 1.27–15.85). Significant associations were also present for constipation (OR = 3.43), dizziness (OR = 2.78), and depression (OR = 2.31). There were no significant associations with tremor, shoulder pain or stiffness, neck pain or stiffness, fatigue, insomnia, sleep apnea, anxiety, restless legs syndrome, Raynaud's and erectile dysfunction. Ataxia was present in 7 patients with MSA and no controls, and joint stiffness only in one control and no patient with MSA (Table 2).

Six of these diagnoses were also significantly associated with subsequent MSA in the time period 2–5 years prior to the index date: balance impairments (OR = 15.34; 95% CI: 2.00–117.76), dizziness (OR = 7.76; 95% CI: 2.64–22.76), constipation (OR = 3.21; 95% CI: 1.24–8.31), and depression (OR = 1.98; 95% CI: 1.01–3.88). There was a strong association with hypotension (OR = 7.77; 95% CI: 0.96–62.95) and urinary dysfunction (OR = 3.86; 95% CI: 0.81–18.49), but these associations only reached p-value between 0.05 and 0.10 (tendency) (Table 2).

In the time period 5–10 years prior to the index date, only depression (OR = 3.82; 95% CI: 1.32–11.01) was significantly associated with MSA. Due to the small patient samples, the strong association of constipation with MSA (OR = 7.10; 95% CI: 0.85–59.32) was not significant (Table 2).

4. Discussion

Our data for the first time show the pre-diagnostic presentations of patients with a later diagnosis of MSA in a longitudinally collected routine care dataset. Previous retrospective reports in patients with MSA suggested that the earliest features of MSA are often autonomic (in 73%) [2,6,7], including erectile failure, orthostatic hypotension, urinary urgency or hesitancy, and may also include fatigue and REM sleep behaviour disorder (RBD), a high proportion of whom later develop MSA [8]. Motor symptoms have been reported to often occur more closely to the diagnosis and after the onset of autonomic symptoms(4), and in those with the cerebellar subtype of MSA ataxia is typically present at diagnosis. A pattern of initial genitourinary dysfunction followed by orthostatic hypotension and sleep disorders including RBD and sleep apnoea, and respiratory disturbances including excessive snoring and stridor has been suggested [4,6]). Olfactory loss and cognitive impairment [3,6,8,9] on the other hand have been suggested to be relatively rare in the early phase of MSA, unlike in PD where these are reported to be early complaints [10,11].

In this study, we confirmed that hypotension was a frequent and prominent early finding within the 2 year before diagnosis, and the corresponding report of dizziness in the 2–5 years before diagnosis, but neither of them was significantly more common than in controls more than 5 years before diagnosis. Urinary dysfunction frequency was elevated before diagnosis but insufficient numbers for comparison were available for the most distant observation period. Similarly, the ICD-10 code for erectile dysfunction was recorded rarely in both groups. Constipation on the other hand, was elevated in all three observation periods, similar to what has been reported in PD, although this difference failed to read significance in the earliest period. Depression, also a

Table 1
Characteristics of patients with multiple system atrophy and controls.

	Total		With ≥2 years of retrospective data		With ≥5 years of retrospective data		With ≥10 years of retrospective data	
	Multiple system atrophy (n = 250)	Controls (n = 250)	Multiple system atrophy (n = 221)	Controls (n = 202)	Multiple system atrophy (n = 148)	Controls (n = 137)	Multiple system atrophy (n = 74)	Controls (n = 69)
Women (N, %)	139 (55.6)	139 (55.6)	124 (56.1)	114 (56.4)	79 (53.4)	77 (56.2)	39 (52.7)	40 (58.0)
Men (N, %)	111 (44.4)	111 (44.4)	97 (43.9)	88 (43.6)	69 (46.6)	60 (43.8)	35 (47.3)	29 (42.0)
Age at index date (mean, SD)	62.2 (19.9)	62.2 (19.9)	62.6 (19.6)	63.7 (19.3)	64.5 (18.1)	64.5 (18.5)	64.6 (18.4)	65.2 (18.1)

Table 2
Number of patients with defined symptoms prior to the index date and association between defined symptoms and MSA.

	Within 0 to <2 years				≥2 years to <5 years				≥5 years to <10 years			
	Multiple system atrophy (n = 221)	Controls (n = 202)	OR (95% CI)	P value	Multiple system atrophy (n = 148)	Controls (n = 137)	OR (95% CI)	P value	Multiple system atrophy (n = 74)	Controls (n = 72)	OR (95% CI)	P value
Motor dysfunction												
Balance impairments	32 (14.5%)	3 (1.5%)	**11.23 (3.38–37.29)**	**<0.001**	15 (10.1%)	1 (0.7%)	**15.34 (2.00–117.76)**	**0.009**	3 (4.1%)	0 (0%)	[a]	
Tremor	4 (1.8%)	2 (1.0%)	1.84 (0.33–10.17)	0.482	8 (5.4%)	0 (0.0%)	[a]		2 (2.7%)	1 (1.5%)	1.89 (0.17–21.31)	0.607
Joint stiffness	0 (0%)	1 (0.5%)	[a]		0 (0%)	0 (0%)	[b]		0 (0%)	0 (0%)	[b]	
Ataxia	7 (3.2%)	0 (0%)	[a]		3 (2.0%)	0 (0%)	[a]		0 (0%)	0 (0%)	[b]	
Shoulder pain or stiff ness	15 (6.8%)	12 (5.9%)	1.15 (0.53–2.53)	0.727	14 (9.5%)	7 (5.1%)	1.94 (0.76–4.96)	0.166	7 (9.5%)	6 (8.7%)	1.10 (0.35–3.44)	0.874
Neck pain or stiff ness	18 (8,1%)	9 (4.5%)	1.90 (0.83–4.34)	0.126	8 (5.4%)	11 (8.0%)	0.66 (0.26–1.68)	0.378	7 (9.5%)	5 (7.3%)	1.34 (0.40–4.43)	0.634
Restless legs syndrome	2 (0.9%)	3 (1.5%)	0.61 (0.10–3.66)	0.585	2 (1.4%)	1 (0.7%)	1.86 (0.17–20.78)	0.613	0 (0%)	0 (0%)	[b]	
Psychiatric Symptoms												
Memory problems	9 (4.1%)	1 (0.5%)	**8.53 (1.07–67.92)**	**0.043**	4 (2.7%)	0 (0.7%)	[a]		1 (1.4%)	1 (1.5%)	0.93 (0.06–15.19)	0.960
Depression	58 (26.2%)	27 (13.4%)	**2.31 (1.39–3.82)**	**0.001**	29 (19.6%)	15 (11.0%)	**1.98 (1.01–3.88)**	**0.046**	17 (23.0%)	5 (7.3%)	**3.82 (1.32–11.01)**	**0.013**
Anxiety	8 (3.6%)	4 (2.0%)	1.86 (0.55–6.27)	0.317	5 (3.4%)	7 (5.1%)	0.65 (0.20–2.10)	0.470	4 (5.4%)	2 (2.9%)	1.91 (0.34–10.80)	0.462
Insomnia	16 (7.2%)	15 (7.4%)	0.97 (0.47–2.02)	0.942	15 (10.1%)	10 (7.3%)	1.43 (0.62–3.31)	0.400	9 (12.2%)	5 (7.3%)	1.77 (0.56–5.58)	0.328
Autonomic dysfunction and fatigue												
Hypotension	16 (7.2%)	1 (0.5%)	**15.69 (2.06–119.40)**	**0.008**	8 (5.4%)	1 (0.7%)	7.77 (0.96–62.95)	0.055	3 (4.1%)	3 (4.4%)	0.93 (0.18–4.77)	0.930
Urinary dysfunction	14 (6.3%)	3 (1.5%)	**4.49 (1.27–15.85)**	**0.020**	8 (5.4%)	2 (1.5%)	3.86 (0.81–18.49)	0.091	3 (4.1%)	0 (0%)	[a]	
Constipation	21 (9.5)	6 (3.0)	**3.43 (1.36–8.68)**	**0.009**	19 (12.8%)	6 (4.4%)	**3.21 (1.24–8.31)**	**0.016**	7 (9.5%)	1 (1.5%)	7.10 (0.85–59.32)	0.070
Dizziness	33 (14.9%)	12 (5.9%)	**2.78 (1.39–5.55)**	**0.004**	28 (18.9%)	4 (2.9%)	**7.76 (2.64–22.76)**	**<0.001**	9 (12.2%)	5 (7.3%)	1.77 (0.56–5.58)	0.328
Sleep apnea	9 (4.1%)	4 (2.0%)	2.10 (0.64–6.93)	0.223	7 (4.7%)	4 (2.9%)	1.65 (0.47–5.77)	0.432	0 (0%)	3 (4.4%)	[a]	
Raynaud's syndrome	1 (0,5%)	1 (0.5%)	0.91 (0.06–14.70)	0.949	1 (0.7%)	1 (0.7%)	0.93 (0.06–14.94)	0.956	0 (0%)	1 (1.5%)	[a]	
Erectile dysfunction	1 (0.5%)	2 (1.0%)	0.46 (0.04–5.05)	0.521	1 (0.7%)	2 (1.5%)	0.46 (0.04–5.12)	0.527	0 (0%)	0 (0%)	[b]	
Fatigue	5 (2.3%)	4 (2.0%)	1.15 (0.30–4.33)	0.841	3 (2.0%)	6 (4.4%)	0.45 (0.11–1.84)	0.268	1 (1.4%)	2 (2.9%)	0.46 (0.04–5.18)	0.529

[a] Odds ratio cannot be calculated as one of the groups has 0 events.
[b] Odds ratio cannot be calculated as both groups have 0 events.

common pre-diagnostic feature of PD, on the other hand, was significantly more common in the MSA group in all three observation periods, despite lower odds ratios, suggesting a long prodrome of depressive symptoms in MSA. Memory problems were significantly more often found in the MSA group than in controls within the two years before diagnosis of MSA, but rates of anxiety were not consistently elevated. Balance problems were also a common feature before diagnosis of MSA, being up to 15 times more common before diagnosis, except the earliest period where few patients or controls reported this problem. Ataxia occurred only in the group with later diagnosis of MSA but not in controls, in keeping with the specific nature of this finding. Tremor on the other hand was not more common in the MSA group at any time period, as were shoulder pain/stiffness, neck pain/stiffness or insomnia, as these may represent fewer specific features of MSA.

These findings confirm the prominent autonomic involvement in the early stages of MSA, including postural hypotension, constipation, and urinary dysfunction, with early and prominent balance problems and a proportion who have ataxia. Compared to our results in Parkinson's disease study in the same database(11), the differences in the ORs regarding hypotension (OR 15.69 vs 2.28), balance impairments (OR 11.23 vs 3.47), and urinary dysfunction (OR 4.49 vs 2.64) in the 2 years before diagnosis are particularly noticeable.

Of note, depression was the clinical feature most consistently diagnosed more often before the diagnosis of MSA, although a weaker association was found at all time points, suggesting that this is common but not prominent or universal finding in pre-diagnostic MSA. Anxiety on the other hand did not appear to be an early feature of MSA. Memory problems, classically not considered a key feature of MSA, also was significantly more common in the period preceding the diagnosis in keeping with the high frequency of cognitive impairment of MSA now recognised, albeit of milder severity than other features [12]. Other features of established MSA, such as Raynaud's syndrome or sleep apnea, were not found to be increased in the prodrome of MSA in this study and may predominantly occur later in the disease course. Lack of identification of other early features of MSA such as erectile dysfunction or RBD may however be due to underdiagnosis, barriers to coding on the database or patients not seeking advice for these. Numbers of those with longer follow up were overall small reducing power to detect associations, but lack of association except for constipation is also in keeping with a shorter pre-diagnostic period of MSA than in PD in keeping with the faster disease progression in MSA.

4.1. Strength and limitations

We based our analyses on ICD-10 diagnoses in a primary care database, which is likely to have led to underreporting of clinical findings such as RBD or anosmia. In addition, a detailed clinical report of examination findings is not available in this system and, whilst the diagnoses of MSA are likely to have been made by a specialist before being entered in this primary care database, we could not verify whether cases fulfilled diagnostic criteria for MSA. Similarly, we could not confirm precise clinical features of pre-diagnostic presentations. Furthermore, the numbers of patients with MSA in the database were relatively low, in keeping with the incidence of MSA in the general population, but precluding calculation of more robust estimates and examination of rarer possible presentations. Finally, as the time period examined was that before diagnosis of MSA, the study would not have detected any change of diagnosis at a later time point. Nevertheless, this is the first study examining the pre-diagnostic features of MSA in a case control setting in a prospective routine sample using a large database confirming the early and strong association with known early features of MSA but also detecting possible new early presentations.

The results demonstrate thatpresentations that were significantly more common in patients with MSAin the pre-diagnostic phase than in controls were autonomic complaints such as postural hypotension, urinary and bowel dysfunction, and early balance impairment. However, the study also highlights that memory complaints and depression may be early features of MSA years before diagnosis.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.02.003.

References

[1] I. Litvan, K.P. Bhatia, D.J. Burn, C.G. Goetz, A.E. Lang, I. McKeith, et al., Movement disorders society scientific issues committee report: SIC task force appraisal of clinical diagnostic criteria for parkinsonian disorders, Mov. Disord. 18 (5) (2003) 467–486.
[2] J.H. McKay, W.P. Cheshire, First symptoms in multiple system atrophy, Clin. Auton. Res. 28 (2) (2018) 215–221.
[3] M. Moscovich, S. Heinzel, R.B. Postuma, R. Reilmann, T. Klockgether, H. Jacobi, et al., How specific are non-motor symptoms in the prodrome of Parkinson's disease compared to other movement disorders? Park. Relat. Disord. 81 (2020) 213–218.
[4] V. Chelban, D. Catereniuc, D. Aftene, A. Gasnas, E. Vichayanrat, V. Iodice, et al., An update on MSA: premotor and non-motor features open a window of opportunities for early diagnosis and intervention, J. Neurol. 267 (9) (2020) 2754–2770.
[5] W. Rathmann, B. Bongaerts, H.J. Carius, S. Kruppert, K. Kostev, Basic characteristics and representativeness of the German Disease Analyzer database, Int. J. Clin. Pharm. Ther. 56 (10) (2018) 459–466.
[6] M. Jecmenica-Lukic, W. Poewe, E. Tolosa, G.K. Wenning, Premotor signs and symptoms of multiple system atrophy, Lancet Neurol. 11 (4) (2012) 361–368.
[7] A. Lipp, P. Sandroni, J.E. Ahlskog, R.D. Fealey, K. Kimpinski, V. Iodice, et al., Prospective differentiation of multiple system atrophy from Parkinson disease, with and without autonomic failure, Arch. Neurol. 66 (6) (2009) 742–750.
[8] C. Xia, R.B. Postuma, Diagnosing multiple system atrophy at the pre-diagnostic stage, Clin. Auton. Res. 30 (3) (2020) 197–205.
[9] G.K. Wenning, R. Brown, Dementia in multiple system atrophy: does it exist? Eur. J. Neurol. 16 (5) (2009) 551–552.
[10] A. Schrag, L. Horsfall, K. Walters, A. Noyce, I. Petersen, Prediagnostic presentations of Parkinson's disease in primary care: a case-control study, Lancet Neurol. 14 (1) (2015) 57–64.
[11] J. Bohlken, A. Schrag, S. Riedel-Heller, K. Kostev, Identification of pre-diagnostic presentations of Parkinson's disease among primary care outpatients in Germany, Neuroepidemiology 56 (1) (2022) 41–49.
[12] S. Eschlbock, M. Delazer, F. Krismer, T. Bodner, A. Fanciulli, B. Heim, et al., Cognition in multiple system atrophy: a single-center cohort study, Ann. Clin. Transl. Neurol. 7 (2) (2020) 219–228.