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Do selective serotonin reuptake inhibitors improve survival in multiple system atrophy?

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Abstract

Introduction—Loss of brainstem serotonergic neurons in MSA patients is implicated in respiratory dysfunction including stridor and may increase the risk of sudden death. Augmenting serotonergic transmission through selective serotonergic reuptake inhibitors (SSRIs) has been proposed to improve stridor and prolong survival in multiple system atrophy (MSA). We sought to determine whether MSA patients on an SSRI during their disease course have improved survival compared to those not on an SSRI.

Methods—Review of all MSA patients from 1998-2012 at Mayo Clinic, Rochester who completed autonomic function testing. Use of SSRI medications was obtained from patient-provided medication lists in the electronic medical record. Clinical symptoms were collected from patient histories; the presence of stridor was obtained from clinical histories and polysomnogram. Surviving patients were called to assess for stridor and SSRI use.

Results—Of 685 MSA patients, 132 (19%) were on an SSRI. Median time from symptom onset to death was 7.5 years with no difference based on SSRI use ($p = 0.957$). Rates of stridor were similar in SSRI users and non-users based on patient report and polysomnography ($p = 0.494$ and $p = 0.181$, respectively). SSRI use was associated with parkinsonism ($p = 0.027$) and falls ($p = 0.002$). Stridor was similar in SSRI users and those not on an SSRI.

Conclusions—There was no difference in survival in MSA patients on an SSRI. However, SSRI use was associated with higher rates of parkinsonism and falls.

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Keywords

multiple system atrophy; stridor; autonomic; parkinsonism; SSRI

Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure and motor involvement of parkinsonism and/or cerebellar ataxia [1]. Additionally, respiratory insufficiency and stridor are clinical features in MSA which have been attributed to deficits in serotonergic transmission [2-6]. Medullary serotonergic neurons are depleted in multiple system atrophy and this has been implicated as the potential cause of stridor and sudden death in MSA patients [6, 7]. Augmenting serotonergic neurotransmission has been proposed as a neuroprotective strategy [8] while selective serotonin reuptake inhibitor (SSRI) use has been shown to improve laryngeal dysfunction and glottic opening in a few MSA patients [9]. This has major implications as there are no pharmacologic treatments that have been shown to improve survival in MSA. Therefore, we sought to determine whether MSA patients in a large cohort who had received treatment with an SSRI during their disease course had improved survival compared to those who had not received an SSRI.

Methods

All patients with the diagnosis of MSA evaluated at Mayo Clinic, Rochester between January 1998 and December 2012 were retrospectively reviewed. Inclusion criteria included standardized autonomic function testing with tilt table testing. Clinical characterization was performed as previously described [10]. Medication use was determined from electronic patient-provided medication lists and clinical notes. Patients were considered on an SSRI if there was documentation of medications from the SSRI class on their medication profile at any time from MSA symptom onset until death or last follow-up. Living patients were called to assess for development of stridor and SSRI use. Statistical analyses were performed using SAS, version 9.3 (SAS Inc, N.C.), with statistical significance set at $p < 0.05$. Survival analyses using time from symptom onset to death were performed using Kaplan-Meier estimates with survival curves, for patients without a death date, date of last follow-up or last contact was used (censor date).

Results

Of 685 MSA patients, SSRI use was documented in 132 (19%). Demographic and clinical features are shown in Table 1. Of the SSRI users, the majority were women (63.6%). When evaluating all of the women in the study, 25.5% received SSRIs compared to 13.5% of men. When provided, the indication for SSRI was depression (87.9%), anxiety (8.8%), or both depression and anxiety (3.3%). The SSRI medications used are listed in order of frequency: sertraline (24.2%), paroxetine (22.7%), escitalopram (22.0%), citalopram (21.2%), and fluoxetine (9.9%); dosages were not collected.

While there was no difference in MSA subtype among those on an SSRI, parkinsonism was more common in the SSRI users (84.1% compared to 75.0% of non-users; $p = 0.0291$).

Depression was also more common in those with parkinsonism compared to those without parkinsonism (27.4 compared to 18.2%, $p = 0.022$). Falls were more commonly reported in the SSRI group (77.3% compared to 64.4% of non-users; $p = 0.0053$), however, falls were not associated with depression ($p = 0.1675$). Report of orthostatic intolerance was similar between groups. Objectively, systolic blood pressure drop at 5 minutes of head up tilt was less in the SSRI group than those not on SSRIs. Stridor, either by clinical report or polysomnogram confirmation, was similar between SSRI users (28.0%) and non-users (25.1%; $p = 0.5068$).

Overall, median survival was 7.5 years (interquartile range 5.4 to 10.1 years) with no difference in survival in patients on an SSRI compared to those not on an SSRI ($p = 0.957$) (Figure).

Discussion

In our large cohort of MSA patients, there was no difference in survival in MSA patients on an SSRI compared to those not on an SSRI. In contrast, motor features of parkinsonism and falls were more common in SSRI users. Increased falls appear to be related to motor control as neither orthostatic intolerance symptoms or orthostatic hypotension was more common in the SSRI group. In fact, the SSRI group had a less pronounced drop in systolic blood pressure during tilt. Worsening of motor symptoms was noted in MSA patients during the Ozawa study examining glottic opening while on paroxetine, though a possible contribution of paroxetine versus underlying disease progression is unknown [9]. Additionally, the design of this study negates any assumption regarding causation of increased falls and parkinsonism in MSA patients on SSRIs.

The higher rate of parkinsonism among SSRI users may relate to higher rates of depression in MSA patients with parkinsonism features. We did not find falls associated with depression. Our cohort had similar rates of depression in MSA as previous studies [11, 12]. Additionally, SSRI use was similar to United States trends for antidepressant use during the study period with higher SSRI use in women compared to men [13]. One explanation for the higher rate of parkinsonism in the SSRI group may be a higher rate of depression in MSA patients with prominent parkinsonism [14] and the use of SSRIs to treat depressive symptoms. SSRIs have demonstrated efficacy in the management of depression in patients with Parkinson disease (PD) [15]. In randomized controlled trials of SSRIs in PD, worsening motor effects were rare and tended to be associated with citalopram use rather than other SSRIs [15-17]. In MSA patients, paroxetine has been shown to improve limb agility on the United Parkinson's Disease Rating Scale motor examination in a small, double-blind placebo-controlled study though the effect was minor and falls were not assessed [18].

Use of SSRI agents have been considered as a neuroprotective strategy in α -synucleinopathies and MSA [19]. Fluoxetine has been shown to increase neurotrophic factors of glial cell-line derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) in an α -synuclein transgenic mouse model [8] while other potential mechanisms of SSRI neuroprotection include suppression of inflammatory factors [20] and promotion of hippocampal neurogenesis [21]. Pathophysiologically, there is support for the use of SSRIs

in MSA for symptomatic benefit as well. Neuropathological studies show loss of serotonergic neurons in medullary raphe which may contribute to respiratory dysfunction [7]. This specific neuronal loss may impair sensitivity to hypercapnia [22], and impair projections to dilator muscles of the glottis [4] with implications in stridor and the risk of sudden death [6]. However, the effects SSRIs on serotonergic transmission are complex; whereas the increase in synaptic 5-HT due to decrease presynaptic uptake may promote serotonergic actions at the target, they may reduce raphe neuronal activity via inhibitory presynaptic auto receptors.

The Ozawa study of 3 patients evaluated paroxetine at 30 mg per day and observed improved glottic stenosis in 2 patients with an improvement in threshold of airway pressure to maintain glottic opening [9]. We found no difference in clinical report or polysomnogram-confirmed stridor in our patients on SSRIs. However, the patients in our study were on a variety of different SSRI medications and dosages were variable. Perhaps future studies should be directed at SSRI use in patients with polysomnography-confirmed stridor as it may be that those patients benefit. While a prospective trial of fluoxetine in MSA has been completed, results are not yet published [23].

Limitations of this study center on the retrospective nature; however this also led to the advantage of a large number of patients treated with an SSRI during their disease course. Whether patients stayed on SSRI medication through their entire disease course was not captured and patients were classified as SSRI users regardless of duration of therapy. Additionally, there were differences in the type of SSRI prescribed however; the effect of SSRIs is likely a class effect. Doses of SSRIs were also not uniform, contributing to variability.

In conclusion, there was no difference in survival in patients on an SSRI in our retrospective cohort of MSA patients.

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Highlights

- Use of SSRIs has been proposed to improve stridor and prolong survival in MSA.
- In a large cohort of MSA patients, we found no survival benefit in patients on an SSRI.
- SSRI use was associated with higher rates of parkinsonism and falls.

Figure.

Survival curves of MSA patients on an SSRI or no SSRI use.

Censored Kaplan-Meier survival curves for probability of death from symptom onset to death in MSA patients on an SSRI (blue) and not on SSRI (orange). Median survival was 7.5 years with no difference based on SSRI use ($p = 0.957$).

Table 1

Patient demographics and clinical characteristics

	All	SSRI use	No SSRI use	<i>p</i> value ^a
Number (%)	685 (100)	132 (19.3)	553 (80.7)	
Gender				0.0001
Female	329 (48.0)	84 (63.6)	48 (36.4)	
Male	356 (52.0)	48 (36.4)	308 (55.7)	
Age of Onset	60.9 (9.6)	60.0 (9.8)	61.1 (9.5)	0.2475
Probable MSA	594 (86.7)	111 (84.1)	483 (87.3)	0.3199
MSA Subtype				0.3180
MSA-P	430 (62.8)	88 (66.7)	342 (61.8)	
MSA-C	255 (37.2)	44 (33.3)	211 (38.6)	
Parkinsonism	526 (76.8)	111 (84.1)	415 (75.0)	0.0291
Falls	458 (66.9)	102 (77.3)	356 (64.4)	0.0053
Depression	161 (23.5)	78 (59.1)	83 (15.0)	0.0001
Stridor	176 (25.7)	37 (28.0)	139 (25.1)	0.5068
Orthostatic intolerance	460 (67.2)	85 (64.4)	375 (67.8)	0.4711
SBP change at 5 minutes	36.6 (31.3)	32.1 (31.9)	37.7 (31.1)	0.0259

Values displayed are mean (SD) for continuous variables and frequency (%) for categorical variables.

^aBetween SSRI use and no SSRI use

Abbreviations: MSA-C, multiple system atrophy-cerebellar; MSA-P, multiple system atrophy parkinsonism; SBP, systolic blood pressure