Tremor in Multiple System Atrophy – a review

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Abstract

Background: Multiple system atrophy (MSA) is a rare neurodegenerative movement disorder characterized by a rapidly progressive course. The clinical presentation can include autonomic failure, parkinsonism, and cerebellar signs. Differentiation from Parkinson’s disease (PD) is difficult if there is levodopa-responsive parkinsonism, rest tremor, lack of cerebellar ataxia, or mild/delayed autonomic failure. Little is known about tremor prevalence and features in MSA.

Methods: We performed a PubMed search to collect the literature on tremor in MSA and considered reports published between 1900 and 2013.

Results: Tremor is a common feature among MSA patients. Up to 80% of MSA patients show tremor, and patients with the parkinsonian variant of MSA are more commonly affected. Postural tremor has been documented in about half of the MSA population and is frequently referred to as jerky postural tremor with evidence of minipolymyoclonus on neurophysiological examination. Resting tremor has been reported in about one-third of patients but, in contrast to PD, only 10% show typical parkinsonian “pill-rolling” rest tremor. Some patients exhibit intention tremor associated with cerebellar dysmetria. In general, MSA patients can have more than one tremor type owing to a complex neuropathology that includes both the basal ganglia and pontocerebellar circuits.

Discussion: Tremor is not rare in MSA and might be underrecognized. Rest, postural, action and intention tremor can all be present, with jerky tremulous movements of the outstretched hands being the most characteristic. However, reviewing the data on tremor in MSA suggests that not every shaky movement satisfies tremor criteria; therefore, further studies are needed.

Keywords: Multiple system atrophy, Parkinson’s disease, tremor

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Introduction

Multiple system atrophy (MSA) is a fatal, adult-onset, neurodegenerative disease with rapid progression and limited symptomatic treatment options. Clinical features include parkinsonism and cerebellar and autonomic signs and symptoms in various combinations. Two major motor variants are distinguished according to the predominant motor presentation: MSA parkinsonian variant (MSA-P) and MSA cerebellar variant (MSA-C). In Europe and North America, the distribution is in favor of the MSA-P variant, whereas MSA-C is more prevalent in Japan. Neuropathological correlates of MSA-P and MSA-C are striatogniral degeneration and olivopontocerebellar atrophy, respectively.

The clinical presentations of both Parkinson’s disease (PD) and MSA include akinesia and rigidity associated with tremor. The cardinal feature of PD is rest tremor, which is found in more than 70% of patients at disease onset. The classic parkinsonian rest tremor is defined as rest tremor or rest and postural/kinetic tremor of the same frequency. Usually, parkinsonian rest tremor mostly affects a unilateral upper extremity, at least initially, and shows a frequency of 4–6 Hz, whereas the upper frequency can reach up to 9 Hz, especially in early stages of the disease. This kind of rest tremor has a characteristic appearance, with an alternating activation of agonist and antagonist. Typically, the thumb and forefingers move back and forth as if manipulating small objects in the hand; the term “pill-rolling” rest tremor is commonly used when referring to the classic parkinsonian tremor. In PD, rest tremor can also be accompanied by postural/kinetic tremor of a different frequency, and some patients even exhibit isolated postural and kinetic tremors.
The classification of tremor is not as clear in MSA, although postural tremor appears to be more common than rest tremor.\textsuperscript{4,9} Clinical studies have shown that tremor is observed in about one-third of patients during rest and about half of patients during posture, with greater tremor rates in the MSA-P variant compared with the MSA-C variant.\textsuperscript{1,3,10,11} The presence of either rest or postural tremor in association with parkinsonism can cause diagnostic confusion. However, there is evidence that tremor presents differently in MSA versus PD: atypical or jerky components have been reported, and the classic parkinsonian (pill-rolling) rest tremor is only present in a minority of patients (\textapprox{}10\%).\textsuperscript{3,6,12,13} Thus, pill-rolling rest tremor supports a diagnosis of PD. Intention tremor points away from PD but is typical in MSA, especially MSA-C (up to 45\% of patients).\textsuperscript{8} Tremor of the legs, head, chin, lips, and tongue can be found in PD but are all uncommon in MSA.\textsuperscript{14}

To date, little has been written about tremor rates and characteristics in MSA, and few attempts have been made to formulate an MSA tremor classification. Nevertheless, the revised consensus criteria for the diagnosis of MSA include tremor, not further classified, as a feature of possible or probable MSA if occurring in the context of bradykinesia, rigidity, or postural instability.\textsuperscript{15} The classic pill-rolling rest tremor is referred to as a nonsupportive feature, whereas jerky myoclonic postural/action tremor is supportive for the diagnosis of MSA.\textsuperscript{15}

In this review, we systemically analyze the available evidence on tremor in MSA, highlighting features that might improve the differential diagnosis, particularly with regard to PD.

**Methods**

Data for this review were identified by searching PubMed with the terms “multiple system atrophy,” “Parkinson’s disease,” “parkinsonism,” “tremor,” “rest tremor,” “postural tremor,” “action tremor,” “intention tremor,” “myoclonus,” “jerky tremor,” “clinical,” “clinicopathological,” “imaging,” and “neurophysiology.” References from 1900 to 2013 were considered, including case reports and natural history, clinical, clinicopathological, neurophysiological, and imaging studies, summarizing rates of occurrence, site, and tremor and subtype characteristics in MSA patients.

The classification of tremor can be made according to the consensus statement of the Movement Disorder Society, depending on the circumstances under which it occurs.\textsuperscript{2}

**Results**

Ever since documentation of the first MSA cases, tremor has been considered a clinical feature of the disease. Tremor in MSA, formerly known as striatoniagral degeneration, olivopontocerebellar atrophy, or Shy–Drager syndrome, was first mentioned in one of two patients with olivopontocerebellar atrophy in 1900.\textsuperscript{16} In the following case reports by Langston in 1936 and Young in 1944, tremor was not explicitly stated as a distinct feature of parkinsonism.\textsuperscript{17,18} In 1960, Shy and Drager described two patients with orthostatic hypotension and additional parkinsonian features, both of whom showed rest tremor of the hand, and one case also upon movement.\textsuperscript{19} In 1961, Adams and associates reported three striatonigral degeneration patients with an akinetic-rigid syndrome with rest tremor of a frequency of 4–5 Hz.\textsuperscript{20} In addition, ataxia and speech disturbances were accompanied by intention tremor in one patient. In 1973, Aminoff and coworkers evaluated the dopaminergic response of five patients with Shy–Drager syndrome with parkinsonism including tremor; one patient worsened and the other four experienced no improvement.\textsuperscript{21} In 1989, Quinn contributed substantially to the understanding of MSA, stating that “symmetrical onset and absence of classical resting tremor,” which had previously been regarded as features distinguishing MSA from PD, may not be as helpful in making the differential diagnosis because marked and persistent asymmetry and the presence of classical rest tremor had all been reported in pathologically proven MSA.\textsuperscript{22} Instead, Quinn said that irregular jerky postural tremor and myoclonus might represent “red flags” (i.e., clinical features raising doubt about a diagnosis of PD), as they appear to be more common in MSA than PD.

Several clinical and clinicopathological studies in MSA have demonstrated that tremor is not rare in this condition, reporting an overall occurrence of up to 80\% (Table 1).\textsuperscript{4,6,8,10,11,13,15} Comparisons of tremor occurrence in the motor subtypes of MSA have clearly shown that tremor is more common in MSA-P compared with MSA-C (31–83\% for MSA-P and 12–48\% for MSA-C; Table 2).\textsuperscript{4,8,10,11}

**Rest tremor**

Rest tremor is common in MSA, with a frequency ranging from 25\% to 43\% and is more common in patients with MSA-P (32–44\%) compared with MSA-C (17–26\%; Tables 1 and 2).\textsuperscript{4,10,13,24,26} In Europe, the first comprehensive clinical study on MSA, including tremor evaluation, was performed by Wenning and associates in 1994.\textsuperscript{4} This study showed that among 100 probable MSA patients (82 MSA-P and 18 MSA-C), 29\% had rest tremor, including 32\% of the MSA-P cohort and 17\% of the MSA-C cohort. Classic parkinsonian rest tremor with pill-rolling appearance was observed in only 9\% of the entire MSA population (10\% of MSA-P and 6\% of MSA-C patients).\textsuperscript{4} Further clinical investigations by Wullner and colleagues, as well as Rodriguez and coworkers, have reported a rest tremor frequency of 25\% in both MSA-P and MSA-C.\textsuperscript{24,25} Tison and associates reported typical rest tremor rates of 12\%, whereas atypical rest tremor (defined as fast, irregular, or myoclonic) was documented in up to 36\% of MSA patients (for further details, see section “Evolution of MSA tremor”).\textsuperscript{5} The largest MSA cohort investigation to date utilized the European MSA (EMSA) registry and included 437 patients (72\% with a diagnosis of probable MSA, 28\% classified as possible MSA; 68\% MSA-P and 32\% MSA-C) (www.emsa-sg.org), reported a rest tremor frequency of 33\%; the presence of classic pill-rolling tremor was not assessed.\textsuperscript{3} The most recent data are provided by an EMSA natural history study conducted by Wenning and associates, which followed 141 MSA patients (87 MSA-P and 54 MSA-C) for 2 years after symptom onset.\textsuperscript{9} In this study, the rest tremor rate ranged from 35\% to 43\% of MSA patients, with MSA-P patients more commonly affected than those with MSA-C.
Clinicopathological correlations by Wenning and associates in 1995 and 1997, including 35 and 203 pathologically confirmed MSA cases, respectively, support the clinical data; they reported a rest tremor prevalence of 34–39%. Only 8–11% of cases could be classified as classic pill-rolling rest tremor. A clinicopathological study from Australia showed comparable results: despite a rather small study population (n = 12), they reported that 33% of MSA patients had rest tremor.26

In the United States, the North American MSA Study Group (NAMSA-SG) cohort, consisting of 84 probable MSA patients clinically dominated by parkinsonian features, 39% of patients exhibited rest tremor.7 Contrasting results were reported for a clinicopathological investigation of 26 pathologically proven MSA patients (18 MSA-P and 8 MSA-C), in which only 10% of patients showed rest tremor.27 Explanations for these different findings might be the small numbers of patients included or misdiagnoses in prospective studies.

A rest tremor evaluation in a Japanese MSA cohort (18 MSA-P and 31 MSA-C) paralleled the European results, detecting rest tremor in 44% of MSA-P and 26% of MSA-C patients.31 One further study reported lower tremor rates.11

### Table 1. Tremor in MSA

| Study Design | Tremor Type (%) | Ref. |
|--------------|-----------------|------|
|              | Rest | Postural and | Cerebellar | Any | |
|              |      | Action       |            |     | |
| Clinical, prospective, n=100, 82% MSA-P, 18% MSA-C | 29 (9 pill-rolling) | P: 47 (20 jerky) | 15 | 66 | 4 |
|              |      |              |            |     | |
| Clinical, prospective, n=24, 100% MSA-C | 25 | NR | NR | NR | 24 |
| Clinicopathological, n=35, 86% MSA-P, 14% MSA-C | 34 (11 pill-rolling) | P: 29 | 11 | 80 | 13 |
| Clinicopathological, n=203, 60% MSA-P, 28% MSA-C, 12% mixed | 39 (8 pill-rolling) | P: 3 jerky | 24 | 67 | (25 not specified) | 10 |
| Clinical, prospective, n=11, 100% MSA-P | 9 pill-rolling | NR | NR | NR | 29 |
| Clinical, prospective, n=50, 70% MSA-P, 30% MSA-C | 22–36 atypical (12 typical)* | P: 28–50* | 2–32* | 50–62* | 6 |
| Clinical, prospective, NAMSA-SG, n=84, MSA-P>MSA-C | 39 | P: 64 | NR | NR | 7 |
| Clinical, retrospective, n=49, 63% MSA-C, 37% MSA-P | 33 | NR | 39 | 61 | 8 |
| Clinical, retrospective, German Parkinson Net (KNP), n=221, subtypes not specified | 25 | P: 28 | NR | NR | 25 |
| Clinical, prospective, red-flag study, EMSA-SG, n=57, 100% MSA-P | NR | P: 47 jerky | NR | NR | 30 |
| Clinical, retrospective, EMSA registry, n=437, 68% MSA-P and 32% MSA-C | 33 | P: 54 | NR | NR | 5 |
| Clinicopathological, n=43, 12 MSA, 15 PSP, 8 PD and 8 healthy controls | 33 | NR | NR | NR | 26 |
| Clinical, prospective, n=141, 62% MSA-P, 38% MSA-C | 35–43% | 56–67% | NR | NR | 9 |

*At latest follow-up.

Abbreviations: A, action tremor; EMSA-SG, European Multiple System Atrophy Study Group; MSA, multiple system atrophy; MSA-C, multiple system atrophy cerebellar variant; MSA-P, multiple system atrophy parkinsonian variant; NAMSA-SG, North American Multiple System Atrophy Study Group; NR, not reported; P, postural tremor; PD, Parkinson’s disease; PSP, progressive supranuclear palsy.
In summary, rest tremor is present in about one-third of MSA patients, particularly in those with the parkinsonian subtype. It is rarely the pill-rolling type, but this can create a significant diagnostic dilemma.

**Postural tremor and myoclonus**

In general, postural tremor is regarded the most common tremor variant among MSA patients. Its frequency ranges from 28% to 67%, and it is more commonly observed in MSA-P than MSA-C patients (47–55% versus 22%, respectively; Tables 1 and 2).4,8,24,28,30

In contrast to postural tremor in PD, which has been well defined by the Movement Disorder Society,2 there have been few attempts to define this tremor in MSA.

A clinical evaluation by Wenning and colleagues in 1994 revealed postural tremor frequency in 47% out of 100 probable MSA patients, including 52% of MSA-P and 22% of MSA-C patients. A “jerky irregular tremor” was documented in 20% of patients dominated by MSA-P. Moreover, stimulus-sensitive myoclonus of the upper extremity was seen in 31% of patients, more commonly in MSA-P than MSA-C (45% versus 33%).2 In the same year, Rodriguez and his group demonstrated that all but one of 24 MSA-C patients showed reflex myoclonus of the hands/arms on electrophysiological investigation. Unfortunately, clinical evaluation of postural tremor was not documented.24 Shortly after, in 1995, Gouider-Khouja and colleagues performed a comparative study between 18 PD and 18 MSA-P patients.20 They reported jerky postural tremor in 55% of MSA-P patients, of whom 16.6% showed stimulus-sensitive myoclonus clinically. They concluded that, if present, postural tremor is highly suggestive of MSA.20 In a subsequent investigation conducted in the same year, postural tremor was documented in 29% of the total cohort of 35 pathologically confirmed MSA patients; again, the cohort was dominated by the MSA-P presentation (30 MSA-P and five MSA-C patients); clinical myoclonus was also reported in 29% of patients.13

Table 2. Tremor Rates in MSA-P and MSA-C

| Tremor Type                  | MSA-P (%) | MSA-C (%) | References |
|-----------------------------|-----------|-----------|------------|
| Any                         | 31–83     | 12–48     | 4, 8, 10, 11 |
| Rest                        | 32–44     | 17–26     | 4, 8, 24   |
| Classic pill-rolling        | 9–10      | 6         | 4          |
| Jerky/postural              | 47–55     | 22        | 4, 28, 30  |
| Action                      | 22        | 11        | 4          |
| Intention                   | 11–28     | 33–45     | 4, 8       |

Abbreviations: MSA-C, multiple system atrophy cerebellar variant; MSA-P, multiple system atrophy parkinsonian variant.

In 2000, clinical and electrophysiological investigations by Salazar and colleagues revealed that all but 2 of their 11 MSA-P patients who presented with abnormal, small-amplitude, nonrhythmic movements of the fingers or hands when holding a posture or at the beginning of an action showed evidence of “minipolymyoclonus.”29

In 2008, assessment of clinically useful red flags pointing toward a diagnosis of MSA showed that jerky tremor, defined as “irregular postural or action tremor of the hands and/or fingers with stimulus-sensitive myoclonus,” is a feature that appears more often in MSA-P than in PD (47.4% versus 5.9% of patients, respectively) and therefore serves as a supporting feature of MSA (94.1% specificity).30 However, subsequent analyses of the EMSA registry reported in 2010 made no mention of “jerky tremor”; instead, a postural tremor rate of 54% (68.2% MSA-P and 31.8% MSA-C) was reported.3

A recent clinical evaluation of 141 MSA patients (87 MSA-P and 54 MSA-C) revealed postural tremor rates ranging from 36% to 67% of MSA patients (2-year follow-up after symptom onset).5

In the United States, the NAMSA-SG reported a postural tremor frequency of 64% in 84 MSA patients, with parkinsonism being the predominant motor feature.7

Results of a Japanese clinical study with 142 probable MSA patients (119 MSA-C and 23 MSA-P) showed a contrast with the high frequency of postural tremor in western hemisphere studies. Within these analyses, postural tremor was only assessed in combination with action or rest tremor. The combination of rest and postural tremor resulted in a frequency of 8.7% in MSA-P patients and 1.7% in MSA-C patients. The combination of action and postural tremor accounted for 10.1% of MSA-C and 8.7% of MSA-P patients.11 The reasons for this discrepancy remain unresolved.

Taken together, postural tremor appears to be the most common tremor subtype in MSA, especially in MSA-P. Moreover, a jerky/irregular appearance has been linked to postural MSA tremor, and there is electrophysiological evidence suggesting that these irregular and small-amplitude involuntary movements of the hands and/or fingers correspond to myoclonus rather than tremor.4,9,24,28,30 Furthermore, stimulus-sensitive myoclonus (with or without tremor) of the upper extremity is not rare (found in 16.6–95% of MSA patients).4,24,28,30 The clinical differentiation between jerky postural tremor and myoclonus, especially if both are present, has not always been made, and further studies including a greater number of MSA patients are needed to clarify and characterize tremulous versus myoclonic movements, respectively.

**Intention tremor**

In MSA-C, the typical tremor variant is intention tremor paralleling cerebellar pathology. Wenning and colleagues have demonstrated that intention tremor is present in 15% of all MSA patients.4 Looking specifically at MSA-C patients, intention tremor was documented in one-third of patients, whereas intention tremor was found in only 11% of the MSA-P population.5 Assessment of pathologically proven MSA patients by the same group revealed intention tremor frequencies of 11–24%.13
Longitudinal observations have demonstrated that intention tremor may be present at the initial visit of a patient with MSA (2%) but more characteristically develops throughout the disease course (32%), reflecting the cerebellar dysfunction that develops in more than half of MSA-P and MSA-C patients with disease progression (see section “Evolution of MSA tremor”).

In line with the European findings, a Japanese study including 31 MSA-C patients and 18 MSA-P patients showed intention tremor rates of 45% and 28%, respectively. 8 Neither of the American studies on MSA evaluated intention tremor. 7,27

In summary, intention tremor is supportive of a diagnosis of MSA and in a differential diagnosis of PD, intention tremor is indicative of MSA. It appears more commonly in MSA-C patients, although its presence does not exclude a diagnosis of MSA-P. Intention tremor can be present at symptom onset but more typically develops throughout the disease course. Because of this tendency to develop at later disease stages, intention tremor might not be helpful as a diagnostic marker; however, if present, it is very characteristic of MSA.

Evolution of MSA tremor

Three longitudinal studies have specifically looked at tremor evolution in MSA.6,9,31 The first was performed by Tison and colleagues, who followed 50 MSA patients (15 MSA-C and 35 MSA-P) and 50 PD patients for 4.35 years after disease onset.6 The analyses found that limb tremor as a presenting symptom was 10 times more common in PD than in MSA. In addition, classical pill-rolling parkinsonian tremor was less frequent in MSA than in PD (12% versus 68%, respectively, at initial visit; and 12% versus 74% at follow-up). However, atypical tremor at rest, defined as fast, irregular, or myoclonic, was significantly more common in MSA than PD patients at both the initial visit (22% versus 4%, respectively) and the follow-up examination (36% versus 4%). Postural tremor was significantly more frequent at the initial visit in MSA compared with PD patients (28% versus 6%), but there was no significant difference between the two cohorts at follow-up (50% versus 52%). Action tremor was significantly more common at the initial visit in MSA patients (14% versus 6%) and was even more significant at the follow-up examination (38% versus 16%). Intention tremor was rare in MSA patients at the initial visit (documented in only one patient), whereas 16 patients (32%) exhibited intention tremor at the follow-up visit, reflecting the cerebellar dysfunction that develops in more than half of both MSA-P and MSA-C patients throughout the course of the disease.6 Taken together, this very detailed study demonstrated that limb tremor is more frequent in PD than in MSA as an initial symptom. While MSA patients do exhibit rest tremor, classic parkinsonian rest tremor is uncommon. Furthermore, postural and action tremor are more frequent in MSA at the initial visit, with increasing frequencies during follow-up in both disorders. Action and intention tremor also discriminate between MSA and PD (Table 3).6

Interestingly, an investigation of progression rates of parkinsonism in MSA-P patients (mean 11.8 months following first visit) by Seppi and colleagues, including validated rating scales (Unified Parkinson’s Disease Rating Scale III, Schwab and England Scale, and Hoehn and Yahr Scale), showed that there was a significant decline in motor function at the follow-up visit compared with the initial visit, except for the tremor item, which did not progress in the same pattern as akinesia and rigidity.31

A very recent and detailed longitudinal observation study reported on the progression of tremor subtypes in MSA over 2 years. Both rest and postural tremor were documented, with no significant change in

| Tremor Type      | Initial Visit (%) | Follow-up Visit (%)* |
|------------------|------------------|---------------------|
|                  | MSA | PD | MSA | PD |
| Any**            | 50  | 82 | 62  | 84 |
| Unilateral       | 26  | 56 | 24  | 20 |
| Asymmetrical     | 16  | 12 | 12  | 40 |
| Classic pill-rolling | 12 | 68 | 12  | 74 |
| Atypical rest+   | 22  | 4  | 36  | 4 |
| Postural         | 28  | 6  | 50  | 52 |
| Action           | 14  | 6  | 38  | 16 |
| Intention        | 2   | 0  | 32  | 12 |

*Mean follow-up time was 5.5 years after initial presentation.
**Including upper and lower limbs in terms of unilateral and asymmetric appearance and including postural, rest, action, and intention tremor.
+Defined as fast, irregular, or myoclonic.

Abbreviations: MSA, multiple system atrophy; PD, Parkinson’s disease.

Table 3. Evolution of MSA Tremor (Modified According to Tison et al 2002)
either tremor variant subtype in terms of occurrence over a 2-year follow-up period. Rest tremor rates developed as follows: 35.5% at baseline examination, 43.6% at 6 months, 34.5% at 12 months, 40.8% at 18 months, and 41.9% at 24 months. Similarly, postural tremor showed the following course: 56% at baseline, 63.8% at 6 months, 66.7% at 12 months, 65.3% at 18 months, and 62.8% at 24 months.9,10

These two clinical studies indicate that tremor severity in MSA patients, as well as the occurrence of tremor, do not change throughout the observed time course (1 year in the analyses of Seppi et al and 2 years in the study of Wenning et al).9,31 However, according to the study by Tison and colleagues, disease duration might have an impact on tremor rates, with a tendency for rates to increase for all tremor subtypes (5-year follow-up).6

Tremor correlates in MSA

Neurophysiology. Accelerometer recordings allow evaluation of abnormal movement and differentiation of rhythmic tremor from arrhythmic components. Fourier analysis of the frequency spectra of these accelerometric recordings differentiates tremor from other movement disorders that can seem rhythmic upon initial inspection. Patients with MSA can display a “jerky/irregular” tremor and stimulus-sensitive myoclonus of the hands and fingers. Neurophysiological investigations have demonstrated that jerky postural tremor in MSA consists of small-amplitude irregular oscillations with no predominant peak in the fast Fourier frequency spectrum analyses as found in PD, and it has therefore been proposed that these movements are more compatible with a diagnosis of myoclonus rather than tremor. The term “minipolymyoclonus” was introduced to capture the cortical characteristics of jerky postural tremor in MSA.10,24,32

Neuroimaging. Several imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI) using diffusion-weighted imaging and voxel-based morphometry, fluorodeoxyglucose positron emission tomography (FDG-PET), iodine-123-[1beta-carbomethoxy-3beta-[4-iodophenyl]tropane] single-photon emission computed tomography (beta-CIT-SPECT), and iodobenzomizide (IBZM)-SPECT have been successfully investigated as tools to distinguish MSA from PD.33,34 Significant clinical correlations have been demonstrated between cerebellar ataxia and infratentorial abnormalities, including volume loss of the cerebellum, mesencephalon, and pons, which had previously been demonstrated in a clinicopathological study by Wenning and colleagues.10,35–37

There are controversial data regarding correlations between putaminal abnormalities and parkinsonism. Schrag and associates did not find an association between putaminal atrophy and parkinsonism,38 whereas Wakai and colleagues found a correlation between putaminal atrophy and parkinsonism but not with substantia nigra narrowing.12 Therefore, Wakai and coworkers postulated that putamen volume loss is associated with the clinical manifestation of parkinsonism.

To our knowledge, no imaging studies have specifically correlated tremor and brain imaging abnormalities in MSA. In contrast, it is well established that rest tremor in PD does not correlate with dopamine-transporter imaging.30,39

Neuropathology. Detailed brain regional analyses performed by Wenning and colleagues that investigated the degree of cell loss and gliosis in the substantia nigra, putamen, caudate nucleus, inferior olives, pons, Purkinje cells, dentate nucleus, intermediolateral cell column, anterior horn cells, and spinal cord pyramidal tract failed to show any correlation between cell loss and the presence of rest, postural, and intention tremor in MSA.10 However, the retrospective study design and the limited data quality of some instances likely reduced the power of the study to detect tremor correlates. Another clinicopathological study by Song and colleagues that assessed the severity of regional atrophy, cell loss, and lesion densities between PD, progressive supranuclear palsy, and MSA patients demonstrated that clinical features including rest tremor correlated with tissue loss and the severity of inclusion pathologies.26 In particular, they found an association of rest tremor plus resistance to L-Dopa (1-3,4-dihydroxyphenylalanine) treatment and greater globus pallidus atrophy, and therefore postulated that preservation of the globus pallidus is crucial for the generation of these features.

Therapy

Pharmacological therapy. Tremor in MSA is not a major therapeutic target; akinesia-rigidity and dysautonomia are the most disabling symptoms. Even so, there have been very few randomized controlled trials in MSA as compared with PD.

Almost 40% of MSA patients respond to relative high doses of L-Dopa (up to 1,000 mg/day) in the early stages of disease.4,5,9,39,40 However, the beneficial effects disappear after a few years, and disabling dyskinesias occur in half of patients. Dopamine agonists represent second-line drugs that can be used if side effects, such as orthostatic hypotension and psychiatric symptoms, are tolerated. About 10% of MSA patients have a good initial response to bromocriptine and lisuride dopamine agonists.41,42 Other dopamine agonists can also exert initial beneficial effects, although no controlled trials have been performed. However, L-Dopa-responsive MSA patients show a more pronounced benefit regarding akinesia and rigidity compared with rest or postural tremor, which is comparable with PD. Dopaminergic drugs have no effect on cerebellar tremor.

No benefits on parkinsonian features, including tremor, have been reported with anticholinergics, which are commonly used in patients with MSA to treat hypersalivation.

Three studies on a small number of MSA patients have shown that amantadine improves parkinsonian symptoms, including tremor, in a few patients.13,43,44 A beneficial effect was noted on movement initiation and completion in patients with olivopontocerebellar atrophy; there are no reports on other cerebellar symptoms, including tremor.45

Despite the lack of randomized studies, some beneficial effect can be expected on predominant postural tremor with nonselective beta-blockers, such as propranolol.
A possible benefit can also be seen with clonazepam for MSA patients with jerky action or intentional tremor. There are no reports on the use of botulinum toxin for MSA-associated tremor; however, focal limb dystonia with contractures might improve.\textsuperscript{14}

Surgical therapy. Medial pallidotomy failed to improve symptoms in patients with striatonigral degeneration. Bilateral subthalamic stimulation was reported to improve parkinsonism in four patients with MSA-P, with the main benefits observed for rigidity and parkinsonism.\textsuperscript{46} However, other authors have reported deleterious effects of deep brain stimulation.

At present, surgical therapy is not considered an effective therapeutic tool in the routine management of patients with MSA.

**Discussion**

This review of the published data on tremor in MSA, including case reports and clinical, clinicopathological, neurophysiological, and imaging studies, demonstrates that postural tremor is the most commonly reported tremor type in MSA. It is documented in more than half of patients at some point, followed by rest and intention tremor, depending on the motor subtype of MSA and the disease stage.\textsuperscript{1–7} Generally, patients with MSA-P are more frequently affected by tremor than those with MSA-C.\textsuperscript{2,4,10} Jerky/irregular involuntary movements, predominantly of the hands and fingers, are characteristic when MSA patients are maintaining a posture. Considering that the definition of tremor requires the presence of rhythmic, oscillatory movements, predominantly of the hands and fingers, that are characteristic when MSA patients are maintaining a posture. Considering that the definition of tremor requires the presence of rhythmic, oscillatory, involuntary movements, the term “jerky/irregular tremor” does not satisfy these criteria; therefore, on electrophysiological grounds, the term “minipolymyoclonus” might be more appropriate. In fact, myoclonus, reported independently of postural tremor, is not rare in MSA, and these tremor-like movements might be confused with tremor in a clinical setting. To date, the classic parkinsonian rest tremor with pill-rolling appearance has been considered to point toward PD and away from atypical parkinsonism, including MSA. However, it has been demonstrated that typical parkinsonian rest tremor can also occur in patients with postmortem-proven MSA.\textsuperscript{10,13} Therefore, the occurrence of rest tremor can be a cause of diagnostic failure in patients with additional symptoms suggestive of MSA. Moreover, similar to postural tremor, rest tremor in MSA can be atypical, with irregularity or myoclonic elements. Intention tremor as a typical feature of cerebellar involvement is also characteristic of MSA-C and more common in MSA-C, although it can also emerge in patients with MSA-P. Typically, patients with MSA can exhibit more than one kind of tremor owing to the complex neuropathology that includes both the basal ganglia and pontocerebellar circuits.

Therapeutic approaches in patients with MSA mainly target akinesia and rigidity. In general, tremor receives less attention in these patients, and treatment options are very limited because of the low response rate to L-Dopa and other dopaminergic substances. Postural and action tremor, if severe and interfering with goal-directed movements, might respond to benzodiazepines, such as clonazepam, although no reports have been published on this topic. Intention tremor is refractory to drug treatment, similar to in other etiologies causing intention tremor, such as multiple sclerosis.\textsuperscript{47}

In summary, tremor is not rare in MSA. However, the documentation of this condition is not standardized, and there is a lack of detailed characterization of tremor in MSA despite its high prevalence among MSA patients. Clearly, not every shaky movement is a tremor, and distal myoclonic jerks in MSA patients might masquerade tremor more commonly than previously thought. Nevertheless, these atypical characteristics of tremulous movements upon rest and posture in MSA can help to differentiate between PD and MSA. Further studies are needed to address the multifaceted nature of tremor in MSA.

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Kaindlstorfer C, Granata R, Wenning GK Tremor in MSA – a Review

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**Appendix: Assessment of Tremor in MSA According to the Unified Multiple System Atrophy Rating Scale**

In the clinic, tremor in MSA patients is evaluated with the motor part of the Unified MSA Rating Scale (UMSARS). Both rest and action tremor are considered. Rest tremor is scored as follows: 0, absent; 1, slight and infrequently present; 2, mild in amplitude and persistent, moderate in amplitude but only intermittently present; 3, moderate in amplitude and present most of the time; and 4, marked in amplitude and present most of the time. Action tremor is evaluated with respect to postural components, including examination of the patient with outstretched arms (A) and intention components, including examination of tremor on finger pointing (B). The maximal tremor severity is scored on both tasks, and which limb is more affected is documented. The scoring is as follows: 0, absent; 1, slight tremor of small amplitude (A), no interference with finger pointing (B); 2, moderate amplitude (A), some interference with finger pointing (B); 3, marked amplitude (A), marked interference with finger pointing (B); and 4, severe amplitude (A), finger pointing impossible (B).

**Documentation of tremor**

At the first visit, a handwriting sample can be taken from the patient in case of action tremor. During follow-up, in addition to the clinical examination including the UMSARS, drawing of the Archimedes spiral and a second handwriting sample can be recorded to evaluate disease progression and response to therapy, respectively.