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Rest and other types of tremor in adult-onset primary dystonia

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ABSTRACT

Introduction Knowledge regarding tremor prevalence and phenomenology in patients with adult-onset primary dystonia is limited. Dystonic tremor is presumably under-reported, and we aimed to assess the prevalence and the clinical correlates of tremor in patients with adult-onset primary dystonia.

Methods We enrolled 473 consecutive patients with different types of adult-onset primary dystonia. They were assessed for presence of head tremor and arm tremor (rest, postural and kinetic).

Results A total of 262 patients (55.4%) were tremulous: 196 patients presented head tremor, 140 patients presented arm tremor and 98 of them had a combination of head and arm tremor. Of the 140 patients with arm tremor, all presented postural tremor, 103 patients (73.6%) presented also a kinetic component, whereas 57 patients (40.7%) had rest tremor. Rest tremor was unilateral/asymmetric in up to 92.9% of them. Patients with segmental and multifocal dystonia were more likely tremulous than patients with focal dystonia. Dystonic symptoms involving the neck were more frequently observed in patients with head tremor, whereas dystonic symptoms involving the arms were more frequently observed in patients with arm tremor.

Discussion Here we show that tremor is a common feature of patients with adult-onset primary dystonia. It may involve different body segments, with the head being the most commonly affected site. Arm tremor is also frequent (postural>kinetic>rest), occurring in up to one-third of cases. There is a suggestion of a stronger tendency for spread of dystonic features in patients with associated tremor. Dystonic tremor is under-reported and this underscores the importance of careful clinical examination when assessing tremulous patients without overt dystonia.

INTRODUCTION

Rest tremor is defined by tremor that occurs in a body part which is completely supported against gravity. It is mostly found in Parkinson's disease (PD) but can be less frequently seen in other conditions, such as essential tremor (ET) and dystonia.¹ Although there is a consensus stating that tremor and dystonia can be associated,¹ little is known regarding tremor prevalence and phenomenology in patients with adult onset primary dystonia (AOPD) and only one study has focused on its characteristics in a large cohort of patients with AOPD so far.² The authors found that tremor is a relatively common feature, being postural or postural/

kinetic in nature and occurring in about 17% of patients with AOPD. Interestingly, none of their patients had rest tremor, thus suggesting that it is an almost non-existent phenomenon in AOPD. However, this is not our experience.^{3–5} We have indeed identified rest tremor in a number of our patients with cervical and other forms of adult onset dystonia,^{3–5} but literature on dystonic tremor is still poor.

The present study was therefore designed to assess prevalence and clinical correlates of rest and other types of tremor in a large cohort of patients with AOPD.

PATIENTS AND METHODS

We prospectively assessed consecutive patients with a diagnosis of AOPD attending the botulinum toxin clinic at the National Hospital for Neurology and Neurosurgery, London, UK, between April 2010 and December 2012. Part of this cohort (approximately 55%) has been already been described.⁶ This study is selectively based on the clinical information and investigations carried out as part of the routine clinical care of the patients. It has been therefore structured as a clinical audit and, as such, our institution does not require ethics committee approval. All patients had a clinical diagnosis of primary dystonia according to current criteria.⁷ Patients with secondary dystonia were not included. For the current audit, we included patients, who have been assessed by one of the authors at least 3 months after their last set of injections. Patients have been classified as having focal dystonia (cervical dystonia, cranial dystonia, or writer's cramp); segmental dystonia (cranio-cervical dystonia or neck/arm dystonia), and multifocal dystonia (arm dystonia plus cranial involvement).⁷ None of them had lower-limb involvement. The assessment of tremor included observation of head tremor (seated upright, with the head in neutral position and while turning the head to either side), and arm tremor (rest tremor-arms relaxed in the lap; postural tremor-arms outstretched in pronation and supination; flexed postural tremor-shoulders abducted and elbows flexed, placing both hands, palms down, in front of the chest; kinetic tremor-performing the finger-to-nose manoeuvre, writing a standardised sentence and drawing a spiral). Each condition lasted approximately 15 s. If tremor was present for at least 50% of each condition, patients were classified as tremulous, accordingly. Following current recommendations,¹ tremor was defined as a rhythmic/semirhythmic involuntary oscillatory

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movement of a body part. Irregular amplitudes and superimposed jerks, recognised as characteristic of dystonic tremor,¹ were accepted, but patients with isolated head jerks, were not classified as tremulous.

Statistical analyses were performed with the STATA software, V11.0 (StataCorp LP, USA), using t test, χ^2 test, or analysis of variance as appropriate, and deeming p values of less than 0.05 statistically significant.

RESULTS

A total of 473 patients with AOPD were included in the current study. Two hundred and sixty-seven patients had focal dystonia (207 patients with cervical dystonia, 32 patients with cranial dystonia and 28 patients with writer’s cramp), 135 patients had segmental dystonia (54 patients had cranio-cervico dystonia and 81 patients had neck and arm involvement) and 71 patient had multifocal dystonia (cranial dystonia plus arm involvement). Demographic and clinical characteristics are detailed in table 1.

A total of 262 patients (55.4%) were classified as tremulous: 140 patients (29.6% of the entire cohort) presented arm tremor, and 196 patients (41.4% of the entire cohort) presented head tremor. Among tremulous patients, approximately one-third (98 patients) had a combination of head and arm tremor. Of the 140 patients with arm tremor, all presented postural tremor, 103 patients (73.6%) presented also a kinetic component, whereas 57 patients (40.7%) had rest tremor. Among the latter, rest tremor was unilateral in 40 patients (70.2%) and bilateral in 17 patients (29.8%), of whom 13 (76.5%) showed an asymmetric tremor. All types of tremor were found to be more frequent in patients with multifocal and segmental dystonia than in patients with focal dystonia ($p < 0.01$, table 1). Among those with focal dystonia, head and arm tremor were more prevalent in patients with cervical dystonia than in patients with cranial dystonia and with writer’s cramp (48.3% vs 21.8% 12%, respectively, χ^2 test, $p < 0.01$). Details on the pattern of dystonic symptoms in relation to localisation of tremor are given in table 2.

Dystonic symptoms involving the neck were more frequent in patients with head tremor, whereas dystonic symptoms involving the arms were more frequent in patients with arm tremor ($p < 0.01$, table 2). The two groups did not differ with regard to age, disease duration and gender distribution.

DISCUSSION

Tremor is a common feature among patients with AOPD, with arm and head tremor occurring in 30% and 40% of cases,

Table 2 Clinical characteristic of our patients according to localisation of tremor

| | Patients with head tremor | Patients with arm tremor | Patients with head and arm tremor | p Value |
|------------------------------------|---------------------------|--------------------------|-----------------------------------|---------|
| Number | 98 | 42 | 98 | – |
| Sex (F:M) | 76:22 | 33:9 | 78:20 | 0.19 |
| Age, years, mean (SD) | 60.3 (12.5) | 63.1 (13.7) | 62.7 (11.8) | 0.55 |
| Age at onset, years, mean (SD) | 43.18 (12.8) | 46.3 (11.8) | 45.9 (12.1) | 0.29 |
| Disease duration, years, mean (SD) | 17.2 (12.9) | 16.7 (13.2) | 15.9 (12.5) | 0.65 |
| Distribution of dystonia | | | | |
| Cervical, n (%) | 75 (76.5) | 65 (45.7) | 79 (80.6) | 0.0001 |
| Cranial, n (%) | 23 (23.4) | 11 (26.2) | 22 (22.4) | 0.13 |
| Brachial, n (%) | 24 (24.4) | 26 (61.9) | 59 (60.2) | 0.0001 |

respectively. Previous studies have reported tremor frequencies ranging from 7% to 70% in AOPD.^{2 8–10} Such a huge discrepancy between studies might be due to several factors, including small patient samples, with focus on only one type of focal dystonia, and use of medical chart reviews rather than clinical examination to detect tremor. Intriguingly, the largest study which specifically addressed this question in 429 AOPD patients, found postural or postural/kinetic tremor in 16.7% of the cases, while none had rest tremor.² We do not believe that methodological issues can explain such discrepancy: similarly to Defazio *et al*, we have, in fact, clinically assessed consecutive AOPD patients, with the specific aim to look for tremor and its characteristics.

Dystonic tremor is a relatively new category in tremor classification.¹ It is very likely under-recognised and might be mistaken as ET or even PD, depending on the tremor type and distribution. This relies on the lack of markers for the differential diagnosis of tremulous condition, and highlights the difficulty with the clinical diagnosis of dystonia. Among tremulous disorders, ET is undoubtedly overdiagnosed.¹¹ In fact, a review of 350 patients supposed to have ‘pure ET’ has disclosed associated dystonia, including cervical dystonia, writer’s cramp, spasmodic dysphonia, and cranial dystonia, in half of them.¹² The suggestion that dystonic patients are frequently misdiagnosed as ET has been further confirmed by others.¹³ This may also depend on the fact that tremulous dystonic patients may have such

Table 1 Clinical characteristic of our patients

| | Focal dystonia | Segmental dystonia | Multifocal dystonia | p Value |
|-----------------------------------|---|---|---|--|
| Number of patients | Total 267 Cervical dystonia 207 Cranial dystonia 32 Writer’s cramp 28 | Total 145 Cervico-cranial dystonia 54 Cranial/neck/arm 91 | Total 61 | – |
| Age at onset (years, mean±SD) | 42.3±11.9 | 40.7±14.3 | 41.6±12.5 | 0.45 |
| Disease duration (years, mean±SD) | 14.7±8.7 | 21.4±10.1 | 23.5±9.3 | 0.09 |
| Sex (female/male) | 203/64 | 109/36 | 42/19 | 0.63 |
| Head tremor (n) | 72 | 80 | 44 | 0.0001* |
| Arm tremor (n) | Total 38 Postural 38 (asymmetric in 18) Kinetic 24 (asymmetric in 20) Rest 11 (asymmetric in 10) | Total 74 Postural 74 (asymmetric in 45) Kinetic 58 (asymmetric in 48) Rest 28 (asymmetric in 26) | Total 28 Postural 28 (asymmetric in 14) Kinetic 21 (asymmetric in 17) Rest 18 (asymmetric in 17) | 0.0001* 0.0001* 0.0001* 0.0001* |

*Segmental and multifocal versus focal.

confounding clues as autosomal dominant familial history and alcohol responsiveness.⁶

With regard to head tremor, Agnew *et al*¹⁴ have recently shown that in ET cases it may represent a postural tremor that dissipates when patients lie down, whereas in patients with cervical dystonia (CD), head tremor more often persists. Such a phenomenon was not tested during our audit, but we think it may be unwise to consider ET in subjects with isolated head tremor, or in whom head tremor is more severe than their arm tremor.¹⁵ In fact, Louis *et al* studied the prevalence of 'isolated head tremor' among 583 ET patients, and did not identify any case of head tremor in complete absence of arm tremor, and only 2.7% of cases with head tremor and only mild arm tremor.¹⁶ This confirms previous findings by Bain *et al*¹⁷ among 20 families with three-generational pure ET. Patients with PD may seldom present with head tremor, but it is usually not a feature of PD and has been very rarely described.¹⁸ Moreover, we have demonstrated that head tremor is much more common in dystonic patients than in PD cases.⁵ All these evidences suggest that head tremor is rather suggestive of concomitant dystonia.

With a view to rest tremor, it is highly suggestive of PD, but here we show that it may occur in up to 40% of tremulous dystonic patients (meaning approximately 12% of all patients with AOPD), being unilateral in more than two-thirds of them. In the majority of them (92.9%), rest tremor was asymmetric, if not unilateral. This result is in line with our previous observations that a number of patients with unilateral rest tremor and preserved dopaminergic nigrostriatal pathway (ie, patients supposed to be affected with PD, but having scans *without* evidence of dopaminergic deficit—SWEDDs), have dystonic tremor as per the consensus classification⁴ and also by electrophysiology.⁵ Such tremor characteristics as frequency and amplitude seem to be not useful to differentiate between these two conditions (PD and dystonic patients may indeed both show a tremor at about 5–6 Hz).⁵ However, it is remarkable that none of our patients had re-emergent tremor (ie, a postural tremor that emerges after a variable latency of several seconds) while this phenomenon is commonly seen in patients with PD. On the other hand, rest tremor can be seldom seen in ET, and the existence of an ET-subgroup with associated rest tremor has been suggested.^{1 10} However, a recent study has shown that ET patients with associated rest tremor display a blink reflex recover cycle similar to that detected in dystonic tremor, thus indicating that they may have a dystonic tremor rather than a subtype of ET.¹⁹ Once again, this evidence suggests that tremulous dystonic patients are likely misdiagnosed. This may depend on the fact that dystonic features can be mild and involve body parts not affected with tremor, or even that have not yet appeared.¹⁵

When we compared patients with head versus arm tremor regardless of dystonia classification, we found similar age, disease duration and sex distribution. We also found that dystonic symptoms more frequently involved body regions affected by tremor, suggesting that these two phenomena often coexist. On the other hand, tremor involving body regions which were not affected by dystonic symptoms (ie, 'tremor associated with dystonia' as per consensus classification¹), was less frequently observed.

In our cohort, we have found patients with segmental or multifocal dystonia to be more likely tremulous than patients with focal dystonia. This suggests a stronger tendency for spread of dystonic features in patients with tremor, also in line with previous reports.^{2 6} However, whether the presence of tremor in a body segment may anticipate the spread of dystonia in that segment needs to be elucidated in further prospective studies. Moreover, patients with segmental and multifocal

dystonia had a longer disease duration (21 and 23 years, respectively), than patients with focal dystonia (15 years), even though this was not significant ($p=0.09$). On the other hand, tremulous patients had a longer disease duration regardless of the dystonia classification (data not shown), in line with existing literature.⁷ This may suggest that tremor can be a relatively late symptom in patients with AOPD. The long disease duration across the subgroups may also partly account for the discrepancy with previous observations which have included patients with shorter disease duration.⁷ However, we miss data regarding tremor versus dystonia onset. We therefore cannot totally exclude that some patients have developed dystonic symptoms after tremor onset. Moreover, the possibility exists that, at least in some patients, dystonia and tremor are unrelated phenomena, leading to an overestimation bias. However, we believe this is unlikely, given the large sample size.

Neurologists and other practitioners should be aware of the possibility of dystonic tremor. It is frequent in patients with AOPD, with the head being the most common affected site. Arm tremor occurs in one-third of AOPD patients, with or without associated head tremor: arm tremor usually features a postural component, but can be also characterised by kinetic and rest components in some cases. Rest tremor presents more frequently unilaterally (and it is usually asymmetric in patients with bilateral rest tremor), thus it would be wise to consider dystonia even in the differential diagnosis of PD. Our clinical experience would suggest that such features as position/task specificity, jerkiness, presence of tremor-flurries and thumb hyper-extension are fairly typical for dystonic tremor.^{5 15}

We acknowledge some limitations. First, we did not perform electrophysiological recordings, and it may be argued that rest tremor seen in our patients (which was assessed with the arms in semisupination/pronation on their lap) is actually postural tremor that continues when the limb is supported. However, this is a matter of further laboratory research and does not correspond to what is seen in clinical practice. It may be also argued that some patients, particularly those with head tremor, may adopt abnormal head postures in order to compensate or suppress their tremor. This might mislead to the diagnosis of dystonia, but we do not believe this is the case here. Our patients were in fact diagnosed according to established clinical criteria,⁷ and all our CD cases showed restricted head motion due to paradoxical muscle over-activity, which is suggestive of underlying dystonia. As a tertiary centre for movement disorders, we cannot exclude a referral bias. However, we do not believe that this may account for the whole discrepancy between ours and others studies. We would like to remark the importance of careful clinical examination when assessing tremulous patients, looking for dystonic symptoms also in non-tremulous body segments.

Contributors RE: conception, execution, writing the first draft. IR-A: conception, execution, revising the paper. TAS: execution, revising the paper. CC: execution, revising the paper. CG: execution, revising the paper. AB: execution, revising the paper. KPB: conception, supervision, revising the paper.

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