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Mirror Movements in Patients with Essential Tremor

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Abstract

Mirror movements (MM), which occur in age-related neurodegenerative diseases such as Parkinson's disease (PD), have never been studied in essential tremor (ET). The objective of this work is to study the prevalence and clinical correlates of MM in ET cases and controls. In a clinical-epidemiological study in New York, participants performed repetitive motor tasks; MM (hands and feet) were rated. MM occurred in 35/107 (32.7%) ET cases versus 23/97 (23.7%) controls (OR 1.56, $P = 0.16$). Total MM score was 2× higher in cases (3.9 ± 7.7 vs. 1.9 ± 3.9, $P = 0.02$). MM (hands) occurred in 16 (15.0%) cases versus 5 (5.2%) controls (OR 3.24, $P = 0.03$) and total hand MM score was three to four times higher in ET cases (1.4 ± 4.5 vs. 0.4 ± 2.0, $P = 0.03$). MMs were not correlated with age, tremor duration, or severity and were most severe in cases with rest tremor. Thus, it was concluded that MM occurred in 1/3 of ET cases. These results further expand the spectrum of nontremor, motor phenomenology seen in ET. Whether, as in PD, MMs in ET represent a failure of subcortical structures to support the cortical network involved with the initiation of unilateral motor activity, requires future neurophysiological investigation.

Keywords

essential tremor; clinical; mirror movements; Parkinson's disease

Mirror movements (MM) are unintended movements that accompany voluntary activity in homologous muscles on the opposite side of the body.[1] This motor overflow phenomenon often involves the distal upper limbs during alternating or repetitive movements, but may also be observed in the distal lower limbs.[1] They usually occur as mirror reversals of contralateral

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voluntary movements.[2] Although MM may be seen in children, they are considered pathological in adulthood.[2] MM have been described in age-related neurodegenerative diseases such as Parkinson's disease (PD),[3] corticobasal degeneration,[4] and Huntington's disease[5] as well as other neurological disorders, like stroke.[6] Their pathophysiology is unclear, but in other tremor disorders such as PD, might represent a failure of the basal ganglia to support the cortical network that is involved with the initiation of unilateral motor activity.[7]

Essential tremor (ET) is one of the most common movement disorders among adults.[8] Aside from tremor, a variety of other problems of the motor system have been described, including ataxia,[9] slower reaction time,[10] disturbances in visuomotor performance,[11] and impaired motor imagery.[12] Moreover, some of these motor disturbances (especially ataxia) have clinically relevant functional correlates.[9]

To our knowledge, this is the first study of MM in patients with ET, despite the fact that cortical mechanisms have been suggested in ET generation.[13,14] In addition, there are surprisingly few data on the prevalence of MM in normal controls.[3]

The goals of this study were to: (1) estimate the prevalence of MM in ET, (2) examine their clinical correlates (e.g., correlations with tremor severity and duration), and (3) determine whether the prevalence and severity of MM is higher than observed in a comparison group of controls. If, as we hypothesize, these movements are more prevalent in ET cases than controls, there would be a number of implications. First, this would further expand the spectrum of clinical phenomenology associated with ET. It would also provide additional support for the notion that motor phenomenology in ET is not limited to tremor but includes other features. Third, it would raise the possibility that in ET, integration of activity of cortical and subcortical structures in the motor system might be impaired. Finally, it could have functional implications. It has been suggested that MM may contribute to functional disability (due to deficient performance of complex bimanual motor tasks that require independent movements of both hands).[7] Hence, these data could provide other avenues through which one could explore functional disability in ET.[15]

PATIENTS AND METHODS

Subjects

ET patients and controls were enrolled from 2000 to 2008 in an ongoing cross-sectional, clinical-epidemiological study at the Neurological Institute of New York, Columbia University Medical Center (CUMC), Manhattan, New York.[16] Patients came from two primary sources: (1) patients whose neurologist and whose ongoing care was at the Institute or (2) patients who were cared for by their local doctor in the tri-state region (New York, New Jersey, Connecticut) and, as members of the International Essential Tremor Foundation, had read newsletter advertisements for the study. Four additional patients were referred from the Weill Medical College of Cornell University (WMC), Manhattan, New York. All patients had received a diagnosis of ET from their treating neurologist; none had received a diagnosis of PD. Controls were recruited using random-digit telephone dialing. They were ascertained from the same source population as cases and were frequency-matched on age, gender, and race. Before enrollment, cognitive performance was assessed with the 10-min Telephone Interview for Cognitive Status (TICS, range = 0–41 [normal]),[17] and demented participants were excluded. CUMC and WMC Internal Review Boards approved of study procedures; written informed consent was obtained on enrollment.

Evaluation

Cases and controls were evaluated in person by trained testers who administered demographic and medical questionnaires and a videotaped neurological examination.[16] The ET diagnoses were confirmed (E.D.L.) using published diagnostic criteria: (1) either moderate or greater amplitude kinetic arm tremor during at least three of five tests or a head tremor, and (2) the absence of dystonia, PD, or signs of Parkinsonism (excluding rest tremor).[18]

A videotaped neurological examination included an assessment of postural tremor (sustained arm extension) and five tests of kinetic tremor (pouring, drinking, using a spoon, finger-nose-finger maneuver, and drawing spirals). Each of these six tests was performed separately with the dominant and nondominant arms (12 tests total). The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS)[19] was videotaped. In October 2006, an assessment of MM was added to the protocol.

Videotaped postural and kinetic limb tremor was rated (E.D.L.) using a scale from 0 (no visible tremor) to 3 (large amplitude tremor),[16] resulting in a total tremor score (range = 0–36). These 0–3 ratings have been validated against quantitative computerized tremor analysis results (e.g., the correlation [*r*] between the 0–3 rating of dominant arm postural tremor and maximal postural tremor amplitude in the dominant arm during computerized tremor analysis = 0.58, $P = 0.003$).[20] A tremor asymmetry index (range = −1 to +1) was defined as the difference in action tremor ratings between right and left arms divided by the total tremor score. Rest tremor was rated (E.D.L.) using the videotaped motor portion of the UPDRS.[19] Since all ratings were 0 or 1, this was re-coded in the analyses as absent or present. Intention tremor was evaluated (E.D.L.) during the videotaped finger-nose-finger maneuver, as described,[21] and coded as absent or present. Tone was assessed by a trained tester on site.

During the videotaped motor UPDRS examination, participants were seated facing the trained tester, and all limbs were included in the area that was videotaped. Participants were instructed to perform four unilateral voluntary motor tasks with either the right or left hand or foot: finger taps, opening and closing the hand, hand pronation-supination, and ankle flexion-extension foot taps (i.e., eight tasks total). For each task, they were asked to perform at least 10 repetitions with each hand or foot "as quickly as possible." During these activities, their inactive arm was resting in their lap and their inactive foot, planted lightly on the ground. Participants were unaware that our interest was in the resting hand and foot. MM in these were scored (E.D.L.) on the videotape using a three-item scale[1] that included a measure of MM amplitude (range of excursion), distribution (extent to which the movements matched those of the task performing limb), and proportion (fraction of time during which movements were noted) (Table 1). These three items yielded a score from 0 to 10 for each of the eight tasks and a total MM score (range = 0–80) for each participant. The total hand MM score (range = 0–60) was the sum of scores on the six tasks that involved the hands. The total foot MM score (range = 0–20) was the sum of scores on the two tasks that involved the feet. A MM asymmetry index (range −1 to +1) was defined as the difference in MM scores on the right and left sides of the body divided by the total MM score.

Analyses

Analyses were performed in SPSS (Version 16.0). Chi-square tests, *t*-tests, and Pearson correlation coefficients were used to examine group differences. In logistic regression models, which yielded odds ratios (ORs) and 95% confidence intervals (CIs), MM was the dependent variable, and case–control status, the independent variable. In adjusted models, covariates were chosen based on results of univariate analyses.

RESULTS

The 107 ET cases were on average 5.2 years older than the 97 controls but similar in gender, education, handedness, and TICS scores (Table 2). Fifty-eight (28.4%) of 204 participants had MM in either their hands or feet. MMs were not correlated with age, gender or other clinical characteristics (Table 2).

MM of the hands or feet (videotape) were present in 35/107 (32.7%) cases versus 23/97 (23.7%) controls (OR = 1.56, 95% CI = 0.84–2.90, $P = 0.16$), and the total MM score was approximately two-times higher in ET cases than controls (3.9 ± 7.7 vs. 1.9 ± 3.9, $P = 0.02$, Table 3). A total MM score >9.7 was more than two standard deviations above the mean seen in normal controls (Table 3). Sixteen (15.0%) ET cases (including 6/16 [37.5%] with rest tremor and 10/91 [11.0%] without rest tremor) versus 6 (6.2%) controls had such high scores ($P = 0.04$ for comparison of ET cases with controls). MM in the hands were present in 16/107 (15.0%) cases versus 5/97 (5.2%) controls (OR = 3.24, 95% CI = 1.14–9.20, $P = 0.03$) and the total hand MM score was three to four times higher in ET cases than controls (1.4 ± 4.5 vs. 0.4 ± 2.0, $P = 0.03$, Table 3). Adjusting for age, gender, and education did not change the results (e.g., adjusted $OR_{hands} = 3.14$, 95% CI = 1.07–9.23, $P = 0.038$). MM of the feet were present in 28/107 (26.2%) cases versus 19/97 (19.6%) controls (OR = 1.46, 95% CI = 0.75–2.82, $P = 0.27$), and the total foot MM score was nearly 1.7× times higher in ET cases than controls (2.5 ± 4.9 vs. 1.5 ± 3.5, $P = 0.09$, Table 3). MM occurred during more than one task in 16.8% of ET cases versus 8.2% of controls ($P = 0.07$, Table 3).

In the 107 ET cases, presence versus absence of MM in the hands or feet were not correlated with age (65.4 ± 18.5 years with MM vs. 67.9 ± 14.1 years without MM, $P = 0.49$), tremor duration (20.1 ± 17.6 years with MM vs. 22.7 ± 19.3 years without MM, $P = 0.52$), total tremor score (18.0 ± 6.6 with MM vs. 17.3 ± 7.2 without MM, $P = 0.66$), or TICS score (36.1 ± 1.9 with MM vs. 36.1 ± 1.5 without MM, $P = 0.95$). MM were not associated with gender ($P = 0.58$), presence of intention tremor ($P = 0.80$), family history of ET ($P = 0.59$), or family history of PD ($P = 0.18$). When we examined the correlates of the total MM score in 107 ET cases, we obtained similar results (i.e., no correlation between total MM score and each of these factors such as age and gender).

We stratified ET cases based on presence or absence of rest tremor. MM were most common and most severe in ET cases with rest tremor, although the prevalence of MM in the hands remained nearly three times as common in ET cases without rest tremor than in controls (14.3% vs. 5.2%, $P = 0.03$, Table 3) and the total hand MM score was three times higher in ET cases without rest tremor than in controls (1.3 ± 3.7 vs. 0.4 ± 2.0, $P = 0.04$, Table 3).

There was no correlation among ET cases between the tremor asymmetry index and the total hand MM score ($r = 0.06$, $P = 0.56$) or between the tremor asymmetry index and the MM asymmetry index ($r = 0.05$, $P = 0.64$). Indeed, in the four ET cases with unilateral (right) MM, the tremor asymmetry index was low (0.33, 0.03, −0.05, −0.19). Of the two ET cases with unilateral (left) MM, the tremor asymmetry index was similarly low (−0.04, −0.06).

DISCUSSION

In this study of 107 subjects with ET, MMs were common, occurring in approximately one in three cases. Although MM were marginally more common overall (hands and feet) in ET cases than controls (OR = 1.56), and were more severe overall (hands and feet) in ET cases than controls ($P = 0.02$), the most marked case–control difference was in the hands. The prevalence of these movements in the hands was approximately three times higher in ET cases (15.0%) than controls (5.2%). Although MM of the hands were most common in ET cases with rest tremor (18.8%), they were still nearly three times more common in ET cases without rest tremor

(14.3%) than controls (5.2%). In ET cases, neither the presence nor severity of these movements was correlated with age, tremor severity, or tremor duration.

MM are considered pathological in adulthood.[2,7] They may occur in patients with age-related neurodegenerative diseases but also occur in other neurological disorders. The basis for these movements is not entirely clear. In PD, which is another tremor disorder, MM might represent a failure of subcortical structures to support the cortical network involved with the initiation of unilateral motor activity.[22] Whether a similar mechanism is present in ET is not known. Previous work suggests that the cerebral cortex is not normal in ET and that it may be involved in the generation of ET[14]; however, the relationship between these observations and MM in ET is far from clear and neurophysiological investigations are required to explore the basis for MM in ET.

The current findings have several implications. Clinically, they further add to our understanding of the spectrum of clinical phenomenology that may be seen in patients with ET, a disorder that is still diagnosed exclusively on clinical features and that remains mis-diagnosed in as many as 37%[23] to 50%[24] of supposed cases. Second, they provide additional evidence that motor signs in ET are not restricted to tremor but include other features such as ataxia,[9] slower reaction time,[10] disturbances in visuomotor performance,[11] impaired motor imagery,[12] and now, MM. The full functional correlates of several of these signs remain to be determined, but in some case (e.g., ataxia), are very likely to be clinically significant in some individuals. Third, the pathologic anatomy of ET is still an area of limited knowledge and active investigation.[25] These data raise the possibility that in ET, integration of activity of cortical and subcortical structures in the motor system might be impaired. Finally, MM may be a marker of a deficiency in performance of complex bimanual motor tasks,[7] suggesting that they may indeed have functional correlates. This facet would be important to explore, as functional disability is a well-established feature of ET.[15]

There are few data that allow us to compare our findings with other disease states. However, prior studies that have used the same rating system have noted that MM are present in as many as 24 (88.9%) of 27 subjects with early PD,[1] indicating that these movements may be more common in PD than in ET. There are no prior studies of ET cases to which we could compare our results. There are also surprisingly few data on the prevalence of MM in normal controls.[3] In one study, MM were present in 71 (71%) of 100 healthy control subjects;[3] however, differences in methodologies make it impossible to make a direct comparison with our study. More specifically, two of the four voluntary motor tasks were not the same and the rating scales were different.

Fifteen percent of our ET cases had isolated rest tremor (i.e., rest tremor without other features of Parkinsonism). This proportion is well within the range of what has been reported in previous series, with values from those series including 0%,[26,27] 5.9%,[28] 9.9%,[29] 18.8%,[30] and 29.2%.[31]

MM may occur in early Parkinsonism[1] and they mainly occur in the less affected side of patients with early asymmetric Parkinsonism.[32] Some patients with ET may go on to develop PD,[33,34] raising the possibility that some of our ET patients with MM could have had early, undiagnosed PD. Rigidity was examined by trained research personnel rather than a neurologist, so it is conceivable that mild rigidity could have been overlooked in some cases. However, none of our ET cases had bradykinesia or other features of emerging PD (loss of facial expression or diminished arm swing) on the videotaped examination that was reviewed by the neurologist. Nevertheless, it would be useful to collect follow-up data on these ET cases to determine whether any of them were to develop PD in the future. One recent study indicated 3.0% of ET cases developed incident PD over a 3.3-year follow up.[35] Therefore, it is

conceivable that as many as 9.0% of our ET cases could develop PD over the next 10 years. To address this possibility, we conducted sensitivity analyses in which we took the additional conservative step of excluding all of the 15% of ET cases with accompanying rest tremor. Even with this precautionary measure, we found that nearly three times as many of the remaining ET cases had MM in the hands compared with controls, and the severity of these MM was also three times greater than seen in controls, indicating that the MM we observed in ET were not likely the result of diagnostic misclassification.

MM were most prevalent in ET cases with rest tremor (43.8%), but remained approximately one-half of that reported in early PD (88.9%).[1] These data further raise the possibility of links between PD and some cases of ET, as has been raised by others.[36]

There were a number of potential limitations. Our evaluation of MM was by videotaped examination. Although this may have resulted in lower (more conservative) estimates of the prevalence of MM in both cases and controls, the strength of this method is that it allowed videotaped material to be replayed when there was any question about the phenomenology or rating. Our cases were on average 5.2 years younger than our controls; however, MM were not correlated with age.

MM occurred in a sizable minority of ET cases where they were more prevalent and more severe than seen in controls. They were particularly prevalent among ET cases with rest tremor, suggesting that this subset of patients may differ from those without rest tremor. These results further expand the spectrum of nontremor, motor phenomenology that occurs in this disease. Whether, as in PD, MM in ET represent a failure of subcortical structures to support the cortical network involved with the initiation of unilateral motor activity, requires future neurophysiological investigation. Finally, the functional correlates of these movements is unclear; whether these movements portend an underlying deficiency in performance of complex bimanual motor tasks is worthy of future exploration.

LEGENDS TO THE VIDEO

Four ET patients with MM. Patient 1 has mild MM in the right foot (esp. middle toes) while performing ankle flexion-extension taps with the left foot. The ratings[1] were 2 (amplitude), 1 (distribution), and 3 (proportion). Patient 2 has MM of moderate severity of the left hand while opening and closing his right hand. The ratings[1] were 3 (amplitude), 2 (distribution), and 3 (proportion). Patient 3 has clear MM of the right hand while performing hand pronation-supination with the left hand. The ratings[1] were 3 (amplitude), 2 (distribution), and 3 (proportion). Mild tremulousness of the right hand is noted during these movements. While performing ankle flexion-extension taps with the right foot, he has movements of both hands. Patient 4 has mild tremor at rest (right hand) and kinetic tremor of both hands during the finger-nose-finger maneuver. While opening and closing her right hand, there are MM of moderate severity on the left. The ratings[1] were 3 (amplitude), 1 (distribution), and 3 (proportion). There may be some spread to her lips as well, although this is questionable.

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TABLE 1

Scale[1] used to assess severity of MM in the resting hand and foot

Amplitude of mirroring	
0	No movement
1	Barely discernible but repetitive movement
2	Clear movement with excursion of finger, wrist, or ankle of less than 2 cm. Movement is either slight but sustained or stronger but briefer
3	Excursion of finger, wrist, or ankle greater than 2 cm and movement readily distinguished as mirroring (strong and sustained movement)
4	Pronounced mirroring, with amplitude approaching or matching the requested task in the opposite limb
Distribution of mirroring	
1	Less than mirrored task (fewer fingers for instance)
2	Mirroring that involves the same areas as intended task
3	Mirroring spreads beyond the intended task areas
Proportion of mirroring	
1	Mirroring occurs in less than 1/3 of the task intended cycles
2	Mirroring occurs in between 1/3 and 2/3 of the task cycles
3	Mirroring occurs for most of the task cycles (>2/3 of the task cycles)

TABLE 2

Comparison of ET cases versus controls, and participants with MM versus participants without MM

	ET Cases (N = 107)	Controls (N = 97)	MM (N = 58)	No MM (N = 146)
Age (years)	67.1 ± 15.6[a]	72.3 ± 7.7	68.1 ± 15.5	70.1 ± 11.5
Gender (female)	54 (50.5)	58 (59.8%)	34 (58.6)	78 (53.4)
Education (years)	15.6 ± 2.9	15.8 ± 2.9	15.9 ± 2.7	15.6 ± 3.0
Handedness (right)	95 (88.8)	90 (92.7)	51 (87.9)	134 (91.8)
Total tremor score	17.5 ± 7.0[b]	4.5 ± 2.5	12.5 ± 8.6	10.9 ± 8.4
Tremor duration (years)	21.8 ± 18.7	NA	20.1 ± 17.6	22.7 ± 19.3
Tremor at rest	16 (15.0)	NA	7 (12.1)	9 (6.2)
Intention tremor	47 (43.9)	NA	16 (27.6)	31 (21.2)
Family history of ET[c]	62 (57.9)[b]	13 (13.4)	24 (41.4)	51 (34.9)
Family history of PD[c]	5 (4.7)	3 (3.1)	3 (5.2)	5 (3.4)
Telephone interview for cognitive status (TICS) score	36.1 ± 1.6	36.2 ± 1.7	36.3 ± 1.7	36.1 ± 1.7

Values are either means ± standard deviation or number (percentage).

NA, not applicable.

[a] $P < 0.01$ comparing ET cases to controls or comparing participants with MM to participants without MM.

[b] $P < 0.001$ comparing ET cases to controls or comparing participants with MM to participants without MM.

[c] By self-report, one or more affected first-degree relative.

TABLE 3

MM in ET cases versus controls

	All ET cases (N = 107)	ET cases with rest tremor (N = 16)	ET cases without rest tremor (N = 91)	Controls (N = 97)
MM in hands or feet	35 (32.7)	7 (43.8)[a]	28 (30.8)	23 (23.7)
Total MM score (range = 0–80)	3.9 ± 7.7[b]	7.3 ± 11.3[b]	3.4 ± 7.1[a]	1.9 ± 3.9
MM in hands	16 (15.0)[b]	3 (18.8)[b]	13 (14.3)[b]	5 (5.2)
Total hand MM score (range = 0–60)	1.4 ± 4.5[b]	2.6 ± 7.8[b]	1.3 ± 3.7[b]	0.4 ± 2.0
MM in feet	28 (26.2)	6 (37.5)	22 (24.2)	19 (19.6)
Total foot MM score (range = 0–20)	2.5 ± 4.9[a]	4.7 ± 6.5[b]	2.1 ± 4.5	1.5 ± 3.5
MM present during more than one task	18 (16.8%)[a]	6 (37.5%)[c]	12 (13.2%)	8 (8.2%)

Values are either means ± standard deviation or number (percentage).

[a] $P < 0.10$ comparing case groups with controls.

[b] $P < 0.05$ comparing case groups with controls.

[c] $P < 0.01$ comparing case groups with controls.