Published in final edited form as:

J Neurol Neurosurg Psychiatry. 2008 February ; 79(2): 187–189. doi:10.1136/jnnp.2007.131110.

Irregularity distinguishes limb tremor in cervical dystonia from essential tremor

A G Shaikh¹, H A Jinnah¹, R M Tripp², L M Optican³, S Ramat⁴, F A Lenz⁵, and D S Zee¹

¹Department of Neurology, The Johns Hopkins Hospital, Baltimore, MD, USA

²FlexAble Systems, Fountain Hills, AZ, USA

³National Eye Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

⁴University of Pavia, Pavia, Italy

⁵Department of Neurosurgery, The Johns Hopkins Hospital, Baltimore, MD, USA

Abstract

Introduction—Patients with cervical dystonia (CD) often have limb tremor that is clinically indistinguishable from essential tremor (ET). Whether a common central mechanism underlies the tremor in these conditions is unknown. We addressed this issue by quantifying limb tremor in 19 patients with CD and 35 patients with ET.

Method—Postural, resting and kinetic tremors were quantified (amplitude, mean frequency and regularity) using a three-axis accelerometer.

Results—The amplitude of limb tremor in ET was significantly higher than in CD, but the mean frequency was not significantly different between the groups. The cycle-to-cycle variability of the frequency (ie the tremor irregularity), however, was significantly greater (~50%) in CD. Analysis of covariance excluded the possibility that the increased irregularity was related to the smaller amplitude of tremor in CD (ANCOVA: $p=0.007$, $F=5.31$).

Discussion—We propose that tremor in CD arises from oscillators with different dynamic characteristics, producing a more irregular output, whereas the tremor in ET arises from oscillators with similar dynamic characteristics, producing a more regular output. We suggest that variability of tremor is an important parameter for distinguishing tremor mechanisms. It is possible that changes in membrane kinetics based on the pattern of ion channel expression underlie the differences in tremor in some diseases.

The tremor in dystonia is of two types.¹ “Dystonic tremor” is the tremor of a body part affected by dystonia (eg head tremor in patients with cervical dystonia (CD)) and “tremor associated with dystonia” is the tremor of regions not affected by dystonia. Patients with CD often have limb tremor (ie “tremor associated with dystonia”). Clinically, limb tremor in CD is said to be indistinguishable from essential tremor (ET).^{2,3} Cervical dystonia occurs in 0.6–30% of patients diagnosed with ET.^{4–7} Postural and kinetic tremor occur in 4–55% of patients with CD.^{1–3,8–10} Similarly, ET has long been known to show postural and kinetic tremor.^{1,11} But whether or not the tremors of CD and ET are quantitatively similar and share a common pathophysiological mechanism is unknown. To address these questions, we quantified limb

Correspondence to: Aasef G Shaikh, M.D., Ph.D., Department of Neurology, The Johns Hopkins Hospital, 600 North Wolfe Street, Pathology 2-210, Baltimore, MD 21287, USA; aasefshaikh@gmail.com.

Competing interests: None.

tremor with a three-axis accelerometer comparing patients with idiopathic CD and patients with ET (but without CD).

METHODS

This study was approved by the Johns Hopkins Institutional Review Board. Patients with idiopathic CD were recruited from the outpatient clinics. Patients gave informed consent. We excluded patients with CD with a known or presumed cause, more widespread involvement suggestive of segmental or generalised dystonia, or extrapyramidal features suggestive of a neuro-degenerative disorder. Our patients with ET had bilateral, largely symmetrical postural or kinetic tremor of hands. In the group of patients with ET, we excluded patients with dystonia, enhanced physiological tremor, drug-induced tremor, psychogenic tremor or orthostatic tremor.

Limb tremor was recorded from 19 patients with CD and 35 patients with ET, and 18 healthy subjects with a three-axis accelerometer attached with surgical tape to the top of the middle phalanx of the index finger. Patients held their arms out-stretched against gravity with palms toward the floor (postural tremor), comfortably rested their hands on a table in front of them (resting tremor), and performed slow back-and-forth finger-nose-finger movements (kinetic tremor). Typical tremor frequency in ET and CD does not exceed 15 Hz, and we sampled at 100 Hz (more than three times the Nyquist sampling rate). The raw acceleration signal recorded by the three-axis accelerometer contains high-frequency noise, which is inherent in all acceleration sensing systems, and low-frequency noise due to changes in the attitude of the limb relative to gravity (sway). These artifacts were removed by de-trending and digital filtering that involves three-point averaging. The 1 G (9.8 m/s^2) gravity vector was also determined from the 3-D calibration and removed off-line.

Data from each axis of the accelerometer and the composite data (square root of the sum of the acceleration squared for all three axes) were processed separately. Cycle-by-cycle* analysis was performed. The inverse of the cycle width yields the cycle frequency, whereas the difference between the peak and trough gives the oscillation amplitude. Cycles that were tremor were then separated from cycles due to noise or non-tremor (voluntary or involuntary) movements. The separation criteria were based on the definition of tremor as a rhythmic movement with a relatively fixed period and with an amplitude and waveform that is relatively invariant over reasonable periods of time.¹² In this study, a segment of oscillatory movement was called tremor only if the inter-cycle frequency difference among three consecutive cycles was 2 Hz or less. The reliability of the automatic software algorithms was verified by comparing the epochs of the tremor data that were and were not removed.

It is possible that a cycle with a low-amplitude tremor of either a very high or very low frequency could bias the estimate of average tremor frequency. Therefore, amplitude weighting was applied on a cycle-by-cycle basis to calculate average frequency—that is, cycles with low amplitudes have less weight in the frequency determination than cycles with high amplitudes. Amplitude weighting also eliminates the artifacts from adventitious movements to the computation of the mean tremor frequency.

The cycle-to-cycle variability in the frequency of the tremor causes its irregularity (elaborated in the Results and Discussion sections). The absolute frequency of the cycles was normally

*Defining individual cycle: First, we normalised the de-trended data with the mean amplitude (ie normalized amplitude = actual amplitude – mean amplitude). This allows the amplitude to realign along the abscissa and the peaks of the cycles always remain positive and the troughs always negative. The 'x' co-ordinate of the intersection of the data trace (moving from the negative value to the positive value) with the abscissa was recorded. The value of the first data point marks the beginning and the subsequent data points mark the end of the given cycle.

distributed. The normal distribution was determined on the basis of plotting a frequency histogram in each subject during each condition. Therefore, we used the standard deviation of the frequency distribution during the given tremor condition to quantify the tremor irregularity. The process of amplitude weighing does not apply to the computing of the standard deviation of the frequency distribution.

RESULTS

Typical records of postural, resting and kinetic tremor recorded from a patient with CD, a patients with ET and a healthy subject are shown in figure 1A. Patients with CD had pathological postural and kinetic tremor but usually no resting tremor. The weighted mean frequency (MF) and the amplitude of postural, resting and kinetic tremor in patients with CD (black) and patients with ET (grey) is compared in the box and whisker plots in figure 1B. In patients with CD, the MF of postural tremor ranged between 4 and 10 Hz, whereas the MF of their kinetic tremor had a range of 3 to 8 Hz. Notches display the variability of the median between-sample populations. The height of a notch is computed such that box plots with notches that do not overlap have significantly different medians (oneway ANOVA, $p < 0.05$). There was no significant difference in the mean frequencies of postural and kinetic tremor between patients with ET and those with CD ($p > 0.05$, one-way ANOVA; fig 1B). The amplitude of the postural and kinetic tremor in patients with CD was significantly lower than that of those with ET ($p < 0.05$, one-way ANOVA; fig 1C). As in ET, the amplitude of the kinetic tremor in patients with CD was significantly larger than their postural tremor.

Tremor irregularity for postural tremor was approximately 50% greater in patients with CD than in those with ET (fig 1D). The average frequency spread in CD was 1.44 ± 0.45 Hz, which was significantly greater than that in ET (1.0 ± 0.33 Hz) (one-way ANOVA, $p < 0.05$). Tremor irregularity was not significantly different, however, for kinetic (intention) tremor in the two diseases. It is possible that the regularity of tremor may increase with increasing amplitude. If this were the case, then the tremor in patients with CD could be more irregular because it was of lower amplitude. To investigate this possibility, we performed an analysis of covariance (ANCOVA), which takes the magnitude of the amplitude of the tremor into account while analysing the tremor irregularity. The interaction between disease type and tremor amplitude in the ANCOVA indicated a significant difference between the tremor irregularity of ET and CD (ANCOVA, $p = 0.007$, $F = 5.31$). Therefore, the negative correlation between the tremor amplitude and regularity alone cannot account for the irregularity of tremor in CD. Furthermore, the amplitude of tremor in the healthy controls was exceedingly low (data not shown), but the irregularity in tremor associated with CD was significantly larger than that observed in physiological tremor in the healthy controls (fig 1D). Hence, our results suggest that in comparison to ET, the increased irregularity in tremor related to CD is not simply due to its smaller amplitude.

DISCUSSION

Clinical observations and semi-quantitative studies suggest that the limb tremors seen in patients with CD and ET are similar.^{9 10} Our quantitative studies confirmed that the frequencies of limb tremors are similar in CD and ET; tremor amplitude in ET was significantly larger than in CD, although this was not clinically obvious. ANCOVA, which accounts for the dependence of tremor irregularity on tremor amplitude, excluded the possibility that frequency irregularity in CD tremor was due to its smaller amplitude. Therefore, we must look elsewhere for correlates of a larger variability in tremor in CD and one important possibility is in the central oscillators to which abnormal tremor has been attributed.¹²

Pathophysiological considerations: multiple oscillators and greater frequency variability in CD

We hypothesise that, in ET, the tremor arises from multiple oscillators with relatively similar dynamic characteristics and, thus, a more regular output.^{13 14} Conversely, the tremor of CD arises from activity in multiple oscillators with diverse dynamic characteristics and, thus, a more irregular output.

This interpretation raises a core question: What determines the natural frequency of an individual oscillator? Of importance are the synaptic transmission delays between neurons, and the kinetics of membrane ion channels of the neurons within the oscillator circuit. In this scheme, small, yet physiologically plausible, variations in the membrane kinetics of the constituent neurons and differences in synaptic transmission delays among neurons of the two central oscillators could result in minor differences in their oscillation frequency. The larger such a disparity, the greater the frequency spread. A relatively smaller disparity in synaptic delay and in the membrane properties of neurons comprising the abnormal oscillator underlying ET could result in a more regular output and smaller tremor irregularity.^{13 14}

In conclusion, we found that associated (limb) tremor in patients with CD has a greater irregularity than limb tremor in patients with ET. We speculate that differences in synaptic delays and membrane kinetics in central oscillators account for the frequency differences between these two conditions.

Acknowledgments

Funding: Funding was provided by the Gustavus and Louise Pfeiffer Foundation, Ataxia-telangiectasia Children's Project.

REFERENCES

1. Deuschl G, Bain P, Brin M. an Ad Hoc Scientific Committee. Consensus statement of the Movement Disorder Society on tremor. *Mov Disord* 1998;13:2–23. [PubMed: 9827589]
2. Chan J, Brin MF, Fahn S. Idiopathic cervical dystonia: clinical characteristics. *Mov Disord* 1991;6:119–126. [PubMed: 2057004]
3. Couch JR. Dystonia and tremor in spasmodic torticollis. *Adv Neurol* 1976;14:245–258. [PubMed: 941773]
4. Critchley E. Clinical manifestations of essential tremor. *J Neurol Neurosurg Psychiatry* 1972;35:365–372. [PubMed: 5035310]
5. Baxter DW, Lal S. Essential tremor and dystonic syndromes. *Adv Neurol* 1979;24:373–377.
6. Rajput AH, Offord KP, Beard CM, et al. Essential tremor in Rochester, Minnesota: a 45-year study. *J Neurol Neurosurg Psychiatry* 1984;47:466–470. [PubMed: 6736976]
7. Koller WC, Busenbark K, Miner K. the Essential Tremor Study Group. The relationship of essential tremor to other movement disorders: report on 678 patients. *Ann Neurol* 1994;35:717–723. [PubMed: 8210229]
8. Dubinsky RM, Gray CS, Koller WC. Essential tremor and dystonia. *Neurology* 1993;43:2382–2384. [PubMed: 8232962]
9. Deuschl G, Heinen F, Guschlbauer B, et al. Hand tremor in patients with spasmodic torticollis. *Mov Disord* 1997;12:547–552. [PubMed: 9251073]
10. Patterson RM, Little SC. Spasmodic torticollis. *J Nerv Ment Dis* 1943;98:571–599.
11. Lorenz D, Deuschl G. Update on pathogenesis and treatment of essential tremor. *Curr Opin Neurol* 2007;20:447–452. [PubMed: 17620881]
12. Jedyak CP, Bonnet AM, Agid Y. Tremor and idiopathic dystonia. *Mov Disord* 1991;6:230–236. [PubMed: 1922128]

13. Deuschl G, Raethjen J, Lindemann M, et al. The pathophysiology of tremor. *Muscle Nerve* 2001;24:716–735. [PubMed: 11360255]
14. Vaillancourt DE, Sturman MM, Verhagen Metman L, et al. Deep brain stimulation of the VIM thalamic nucleus modifies several features of essential tremor. *Neurology* 2003;61:919–925. [PubMed: 14557560]

Figure 1.

(A) Composite acceleration from a three-axis accelerometer showing postural, resting and kinetic limb tremor in patients with cervical dystonia (CD) and those with essential tremor (ET). Comparison with the normal subject confirms a robust postural and kinetic tremor, but absence of resting tremor in a typical patient with CD. Qualitatively, a typical patient with ET was similar to a patient with CD, but the tremor amplitude was larger. Box and whisker plots of the weighted mean frequency (MF; B) and tremor amplitude (C) from 19 patients with CD (black) and 35 patients with ET (grey) are shown. There was no significant difference in the frequency of postural and kinetic tremor between patients with CD and those with ET. The amplitudes of tremor in ET were significantly higher than in CD. Typically, there is no resting tremor in CD. Whiskers represent the range of the frequency (B) and the amplitude (C) of the tremor. The tops and bottoms of each box are the 25th and 75th percentiles of the observed values, respectively. The distances between the tops and bottoms are the inter-quartile ranges. The horizontal line in the middle of each box is the median. The “plus” symbols beyond the whiskers are outliers. The notch gives the 95% confidence intervals (thus, two boxes with non-overlapping notches are statistically different, $p < 0.05$). Pluses indicate outliers. $\text{mG} = 0.0098 \text{ m/s}^2$. (D) Tremor frequency varies from cycle to cycle. The irregularity in frequency (frequency spread) was quantified by the standard deviation of the single-cycle frequencies. The frequency

spread during postural tremor in patients with CD was significantly higher than in those with ET and in healthy control subjects. Dashed whisker plots represent healthy control subjects. The interaction between disease type and tremor amplitude in the analysis of covariance indicated a significant difference between the tremor irregularity of ET and CD ($p = 0.007$, $F = 5.31$).