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Arm tremor in cervical dystonia differs from essential tremor and can be classified by onset age and spread of symptoms

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Summary

The pathophysiology of arm tremor in patients with cervical dystonia (CD) and its relationship to other types of tremor is unclear. In the present study, we have compared the tremor in these patients with that seen in patients with essential tremor (ET) using two neurophysiological techniques: the triphasic EMG pattern accompanying ballistic wrist flexion movements; and reciprocal inhibition between forearm muscles. During ballistic wrist flexion movements, the latency of the second agonist EMG burst was later in ET than CD patients. This suggests that the mechanism of the arm tremor in CD may differ from that in ET. There was no group difference between reciprocal inhibition in patients with ET or CD. However, there was much more variability in the data from patients with CD. Because of this, we subdivided the CD patients into two groups, group A with normal levels of presynaptic inhibition and group B with reduced or absent presynaptic inhibition. *A posteriori*, it turned out that the patients in these two subgroups had similar clinical symptoms, but different clinical histories. The arm tremor of patients in group A started simultaneously with torticollis (mean onset age of arm tremor 40 years ± 20.7 SD, interval between onset of arm tremor and torticollis 0 ± 2.9 years) whereas it began much earlier (mean onset age 14 years ± 6 SD) and preceded onset of torticollis by a longer interval (21.6 ± 17.5 years) in patients of group B. Patients in group A also had less co-contraction in their ballistic wrist movements between the first agonist and the antagonist burst than those patients in group B. We conclude that arm tremor in patients with CD may have a mechanism different from that seen in patients with ET. Moreover, the data imply that there are two subgroups of CD patients with arm tremor, one with a late and simultaneous onset of arm tremor and torticollis (group A), and another with an early onset of arm tremor and later development of torticollis (group B). These groups do not correspond to the currently proposed clinical subdivision of 'dystonic tremor' and 'tremor associated with dystonia'.

Keywords: arm tremor; ballistic wrist flexion movements; cervical dystonia; essential tremor; reciprocal inhibition

Abbreviations: CD = cervical dystonia; ET = essential tremor; RI = reciprocal inhibition; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale

Introduction

Tremor is a common symptom in many types of movement disorders. It is the only symptom in essential tremor (ET) where it is defined as a bilateral, largely symmetric postural or kinetic tremor involving hands and forearms that is visible and persistent (Deuschl *et al*., 1998). The question we address here is whether the arm tremor seen in ET has the same mechanisms as that seen in another common movement disorder, cervical dystonia (CD).

Many authors have suggested that ET and CD are physiologically and possibly also genetically related, with the implicit assumption that the mechanisms of the tremor are the same in each condition. Thus, CD has been reported

in 0.6–30% of patients with ET (Critchley, 1972; Baxter and Lal, 1979; Martinelli and Gabellini, 1982; Rajput *et al*., 1984; Lou and Jankovik, 1991; Koller *et al*., 1994; Tallón-Barranco *et al*., 1997), whilst postural and kinetic tremor is found in 4–55% of patients with CD (Patterson and Little, 1943; Couch, 1976; Chan *et al*., 1991; Lang *et al*., 1992; Dubinski *et al*., 1993; Deuschl *et al*., 1997, 1998). The arm tremor in CD patients has variously been described as 'enhanced physiological tremor' (Deuschl *et al*., 1997), as 'resembling ET' (Couch, 1976; Chan *et al*., 1991) or being so non-specific as to make the relationship with ET difficult to ascertain (Koller *et al*., 1994).

In contrast to these assumptions of common mechanisms, some authors have emphasized clinical differences between typical ET and arm tremor found in dystonia patients. In particular, tremor associated with dystonia is often irregular, asymmetric and associated with myoclonus (Rivest and Marsden, 1990; Jedynak *et al*., 1991), whereas ET is usually regular and symmetric. However, whether this difference is due to different mechanisms of tremor, or to the influence of dystonia on the expression of tremor is unknown.

In the Consensus Statement of the Movement Disorder Society (Deuschl *et al*., 1998), tremor in dystonia patients has been classified as 'dystonic tremor' when tremor occurs in a body part that is affected by dystonia, e.g. head tremor in torticollis or arm tremor in patients with writer's cramp or dystonic arm posturing, and as 'tremor associated with dystonia' when tremor is present in a body part not affected by dystonia, e.g. hand tremor in CD patients. The latter is often referred to as being 'indistinguishable from mild classic ET' ('ET-like tremor'). This concept implies that 'dystonic tremor' and 'tremor associated with dystonia' ('ET-like tremor') may be different phenomena. It raises the question as to whether the latter but not the former is a form of classic ET. This, of course, would have implications for epidemiological and also genetic studies.

In order to investigate the nature of arm tremor in ET versus that in CD, we have carried out a series of physiological tests in patients with classic ET and compared them with the results from a group of patients with arm tremor and CD. The data show that there are differences between patients with classic ET and patients with dystonia, regardless of whether they have 'dystonic tremor' or 'ET-like tremor'. Additionally, we propose that the division between 'dystonic tremor' and 'ET-like tremor' is modified and replaced with a new subdivision based on reciprocal inhibition findings and age of onset of symptoms.

Material and methods

Subjects

All subjects gave their written informed consent to the study, which was approved by the combined ethics committee of the National Hospital for Neurology and Neurosugery and the Institute of Neurology, London. We studied 11 patients with ET and 19 patients with CD and additional arm tremor. The various components of tremor (rest, postural, kinetic, position or task-specific and intention tremor) were as defined by the Consensus Statement of the Movement Disorder Society on tremor (Deuschl *et al*., 1998).

ET was defined according to the same Consensus Statement (Deuschl *et al*., 1998) as visible and persistent bilateral, largely symmetrical, postural or kinetic tremor involving hands and forearms, with or without additional intention components or tremor in other body parts, but unaccompanied by rest tremor, parkinsonian or cerebellar signs or dystonia. We did not include patients with isolated head tremor since there is some debate over whether this should be classified as classic ET (Deuschl *et al*., 1998).

The diagnosis of CD was made according to published standard criteria (Fahn, 1988). All patients had idiopathic dystonia. We recruited CD patients with visible and persistent postural tremor involving at least the hands and forearms with or without additional kinetic tremor or an intention component, but unaccompanied by rest tremor, parkinsonian or cerebellar signs. According to the tremor consensus statement (Deuschl *et al*., 1998), they were separated into two groups: (i) CD patients with evidence of dystonia (usually action induced) in one or both arms ('dystonic' arm tremor); and (ii) CD patients without clinical evidence of dystonia in the arm ('ET-like' arm tremor).

Patients with a diagnosis of ET were selected randomly from the National Hospital Medical Record database. As arm tremor in CD patients was often not coded in the database, we selected CD patients with postural arm tremor from the botulinum toxin clinic. Over a period of 3 months, CD patients with postural arm tremor were recruited randomly by the treating neurologists in this clinic and were referred for further neurophysiological assessment. None had received botulinum toxin injections for their arm tremor. They were studied at least 2.5 months after their last botulinum toxin injections into neck muscles.

Severity of tremor was scored according to the validated clinical rating scale proposed by Bain and colleagues (Bain *et al*., 1993) which defines four main categories: no tremor (0), noticeable but mild tremor (1–3), moderate tremor, which may be bothersome to the patient but does not lead to significant functional impairment (4–6), severe tremor (7–9), and extremely severe tremor (10). Additionally, disability caused by the arm tremor was assessed by means of a questionnaire proposed by Bain and colleagues (Bain *et al*., 1993). Patients had to rate their impairment on 25 manual tasks. Each task was scored on a 1–4 scale (score of 1 = able to do the activity without difficulty; score of 2 = able to do the activity with a little effort; score of 3 = able to do the activity with a lot of effort; score of 4 = cannot do the activity). Consequently, the minimum disability score was 25 and the maximum 100. The severity of CD was determined using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (Consky and Lang, 1994). The maximum severity score on this scale is 35.

Table 1 *Characteristics of ET and CD patients*

	ET patients	CD patients with arm tremor
Sex (male:female)	6:5	9:10
Age (years) (range)	63 ± 13.7 (42–81)	54 ± 13 (33–76)
Family history of tremor	9 (82%)*	3 (15.8%)
Onset (years) of arm tremor	29.1 ± 15.3	29.8 ± 22.7
Median onset (years)	25	20
Duration (years) of arm tremor	34 ± 17	24 ± 19
Onset (years) of CD	–	40.5 ± 18.5
Duration (years) of CD	–	13 ± 10

Values for age, age of onset and duration are mean ± 1 SD. ET = essential tremor; CD = cervical dystonia. *$P = 0.001$ (χ^2-test).

Patients who were taking drugs for the treatment of their tremor were asked to stop their medication 2 days before the study. All patients were also asked to abstain from beverages containing caffeine on the day of the study.

Experimental methods

Recording system

Patients were investigated seated in a chair. In all experiments, the EMG was recorded from 1 cm diameter silver chloride disc surface electrodes. They were placed in differential pairs 3 cm apart at mid-forearm level over the bellies of the relaxed flexor carpi radialis and flexor digitorum sublimis, and over extensor digitorum communis and extensor carpi radialis. The earth was placed at the wrist. The EMG signals were amplified, analogue filtered (32 Hz to 1 kHz) and acquired at a sampling rate of 5 kHz.

Ballistic wrist flexion movements

The hand (right hand in patients with symmetric, and the more affected arm in patients with asymmetric, postural arm tremor), with fingers extended and forearm semiprone, was placed in a horizontal manipulandum of low inertia pivoted about the wrist joint. Subjects were asked to make wrist flexion movements of 20, 30 and 40° as fast as possible from a starting angle of mild extension. The position of the wrist was measured by a potentiometer connected to the manipulandum and displayed as a vertical bar on the lower half of an oscilloscope screen placed directly in front of the patients. A second, fixed vertical bar on the oscilloscope screen indicated the target position.

Before each movement, the patients were instructed to relax as much as possible. Movements were made to a 'go' command by the investigator. Twenty trials for each size of movement were recorded. Wrist position, velocity, which was derived by electronic differentiation of the position trace, and EMG activity were recorded for each wrist movement and then stored for later analysis.

Each single trial was inspected on the computer screen. The movement amplitude and peak velocities were measured by cursor interaction. Acceleration and deceleration were obtained by differentiation of the velocity trace. The duration of the rectified first agonist burst, and onset latencies of the antagonist and second agonist EMG bursts were measured by cursor interaction. Size of the EMG bursts was obtained by integration of the EMG traces. The duration of co-contraction of the first agonist and antagonist bursts was determined by subtracting the onset latency of the antagonist burst from the duration of the first agonist burst.

Reciprocal inhibition (RI) in forearm muscles

The forearm of patients was pronated and resting on the arm of the chair. H reflexes in the forearm muscles were tested by electrical stimulation of the median nerve in the antecubital fossa. Stimuli of 0.5 ms duration were applied to the median nerve at 5 s intervals to elicit an H reflex in wrist and finger flexors with a minimum direct M response. Stimulus intensity was set to produce an H reflex of half-maximum size. RI of the forearm flexor motor neurones from the antagonist extensor muscle afferents was produced by single, low intensity, electrical stimuli to the radial nerve in the spiral groove. The stimulus intensity was set to be at or just above the threshold of the wrist extensor muscle M response, which was monitored by surface EMG. The median nerve was stimulated 1 and 0.5 ms before, simultaneously with, or 0.5, 1, 2, 5, 10, 15, 20, 25 and 30 ms after the conditioning radial nerve stimulus. Four sets of trials (with 40 stimulations each) were carried out. In each trial, the control condition (median nerve stimulation only) and three different conditioning–test stimuli were randomized, so that each was tested 10 times. Unconditioned and conditioned H reflexes were averaged and their peak-to-peak amplitudes measured. The peak-to-peak amplitude of the conditioned H reflex was expressed as a percentage of the size of the unconditioned H reflex at each time interval.

Statistical analysis

An independent samples *t*-test was used for comparison of normally distributed interval data between subjects. Nominal

Table 2A *Characteristics of CD patients grouped according to clinical tremor classification*

	CD patients with 'dystonic' arm tremor	CD patients with 'ET-like' arm tremor
Sex (male : female)	7 : 5	2 : 5
Age (years) (range)	56 ± 11.8 (38–76)	47.3 ± 8.4 (33–60)
Family history of tremor	1	2
Onset (years) of arm tremor	35 ± 26 (3–71)	22 ± 13.5 (10–45)
Median onset (years)	27	20
Duration (years) of arm tremor	24 ± 22 (1–61)	24 ± 12 (11–43)
Onset (years) of CD	45 ± 19.5 (12–69)	32 ± 14 (10–52)
Duration (years) of CD	13 ± 11 (1–40)	13 ± 8 (3–29)
Interval between onset of arm tremor and CD (years) (range)	11 ± 16 (–5 to 56)	10 ± 15 (0–40)

Values for age, age of onset and duration are mean ± 1 SD. CD = cervical dystonia.

Table 2B *Characteristics of CD patients grouped according to reciprocal inhibition findings*

	CD patients with normal RI (group A)	CD patients with abnormal RI (group B)
Sex (male : female)	2 : 4	3 : 4
Age (years) (range)	53.6 ± 15.1 (38–76)	52.3 ± 13.1 (33–61)
Family history of tremor	1	2
Onset (years) of arm tremor	40 ± 20.7 (10–64)	14 ± 6 (6–20)*
Median onset (years)	40	15
Duration (years) of arm tremor	14.2 ± 8.2 (4–29)	38.2 ± 17.3 (13–61)†
Onset (years) of CD	39.5 ± 19.6 (10–64)	35.6 ± 15 (20–63)
Duration of CD (years) (range)	14.2 ± 7.6 (9–29)	16 ± 11.6 (5–54)
Interval between onset of arm tremor and CD (years) (range)	0 ± 2.9 (–5 to 4)	21.6 ± 17.5 (3–56)‡

Values for age, age of onset and duration of symptoms are mean ± 1 SD; CD = cervical dystonia; RI = reciprocal inhibition; *$P = 0.028$; †$P = 0.01$; ‡$P = 0.013$ (independent samples *t*-test).

data comparisons between subjects were carried out using a χ^2-test (Fisher's exact test for small sample sizes). To measure a possible correlation between different variables, Spearman rank-order correlation coefficient was used. For comparison of results of ballistic wrist flexion movements and RI experiments, repeated measures ANOVA (analysis of variance) was performed. When a significant difference was found in the ANOVA, *post hoc* pair-wise comparison was carried out using Bonferroni correction. For all statistical analysis, an adjusted P value of <0.05 was considered to be significant.

Results

Clinical findings

Demographic data of ET and CD patients with arm tremor are shown in Table 1. Apart from a positive family history of hand tremor, which was significantly more common in ET patients, there were no differences between the groups. The CD patients were subdivided into two groups: those with 'dystonic' and those with 'ET-like' tremor (Table 2A). Arm tremor was significantly more severe in ET patients and CD patients with 'dystonic tremor' as compared with CD patients with 'ET-like' tremor (Fig. 1). Tremor disability scores did not differ significantly between the three groups (Fig. 1). CD severity scores were similar in the two CD groups (mean TWSTRS score of 13.5 ± 3.5 SD and 14.6 ± 4.3 SD in patients with 'dystonic' and 'ET-like' tremor, respectively; not significant). Severity of arm tremor was not correlated with severity or duration of CD in either CD group. There likewise was no correlation between duration of arm tremor and duration of CD.

Ballistic wrist flexion movements

One out of 11 ET patients and two out of 19 CD patients were excluded from data analysis, as these patients were unable to produce fast wrist movements. Figure 2 illustrates a typical example of a rapid, self-paced, self-terminated flexion movement (ballistic movement) at the wrist in a patient with ET and a patient with CD and postural arm tremor. A triphasic pattern of EMG activity in agonist, antagonist and again the agonist muscle can be seen in both patients.

There was no significant difference between the kinematics of the movements made by the two groups (Fig. 3). However,

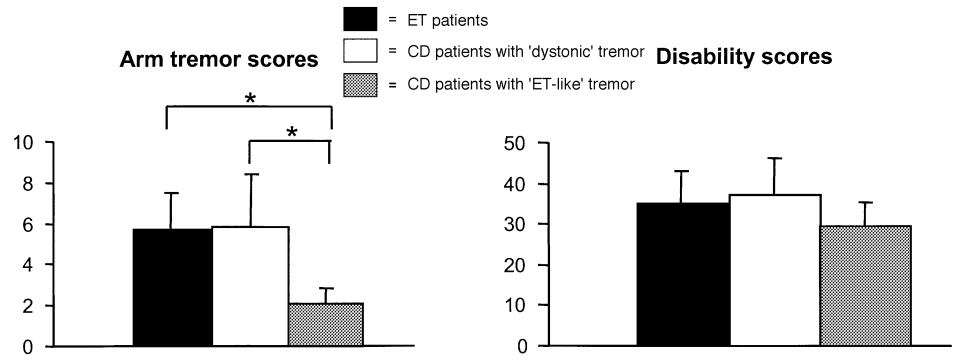

Fig. 1 Arm tremor severity and disability scores of ET and CD patients. *$P < 0.01$ (independent samples *t*-test).

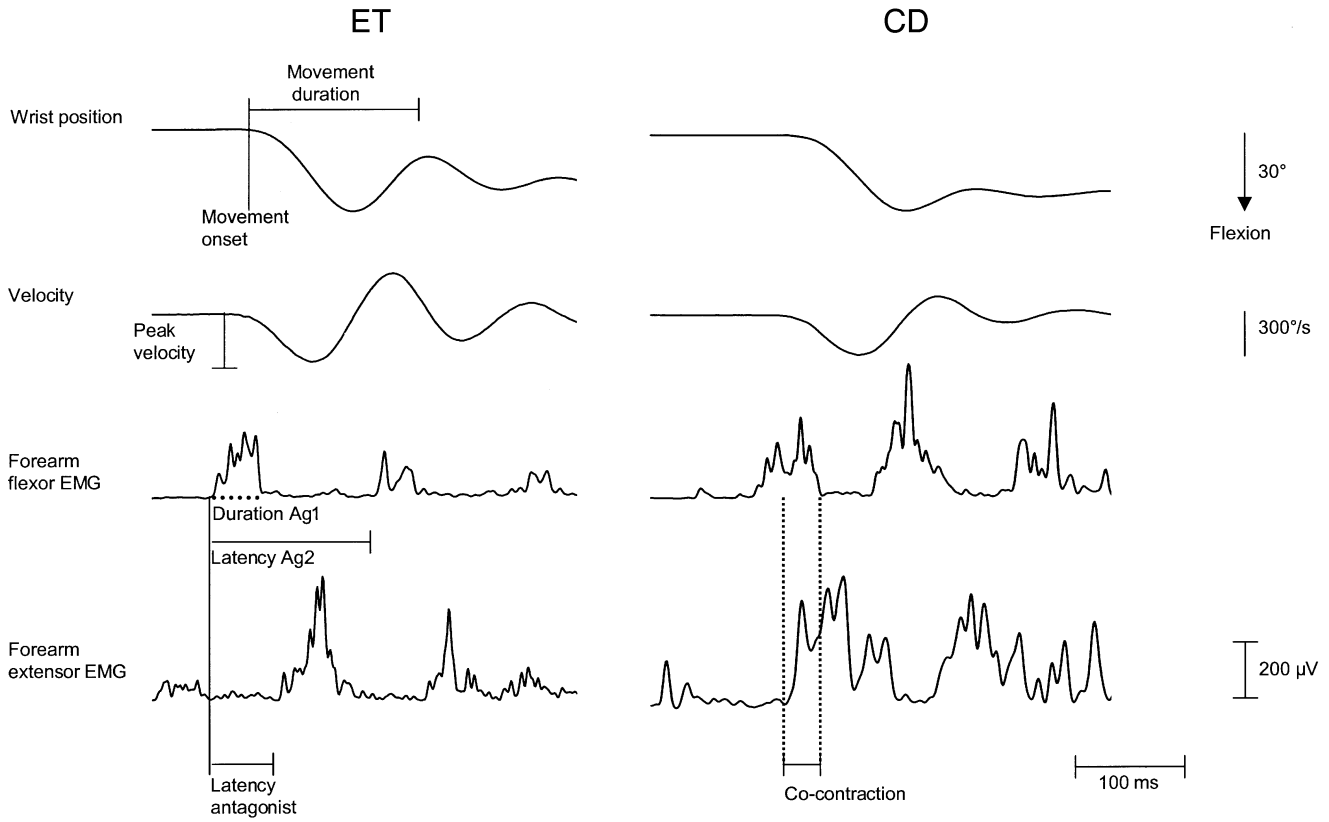

Fig. 2 Representative example of a rapid voluntary ballistic wrist movement in a patient with ET (*left*) and a patient with CD and arm tremor (*right*). A single trial showing the wrist position (top trace) and velocity (second trace) together with the rectified surface EMG activity in forearm flexor (third trace) and extensor (bottom trace) muscles. The typical triphasic EMG burst pattern of activity in the agonist (Ag1), antagonist, and again the agonist (Ag2) can be seen. Note that in the ET patient, the onset of the second agonist burst is delayed and in the CD patient there is a greater amount of co-contraction of Ag1 and the antagonist.

EMG analysis revealed that the onset of the second agonist burst was significantly later in ET patients than in CD patients (Fig. 4). A second analysis was performed comparing ET patients with the 'dystonic' and 'ET-like' subgroups of CD patients. Movement kinematics and EMG patterns did not differ between these two subgroups (data not shown). There was a significant prolongation of the latency of the second agonist burst in ET patients compared with both the 'dystonic' (independent samples *t*-test, $P = 0.008$, across all movement sizes) and the 'ET-like' arm tremor CD subgroup ($P = 0.04$).

RI in forearm muscles

RI could only be evaluated in subjects in whom a reproducible H reflex could be elicited in wrist flexor muscles. Eight out of 11 ET patients and 13 out of 19 CD patients fulfilled this

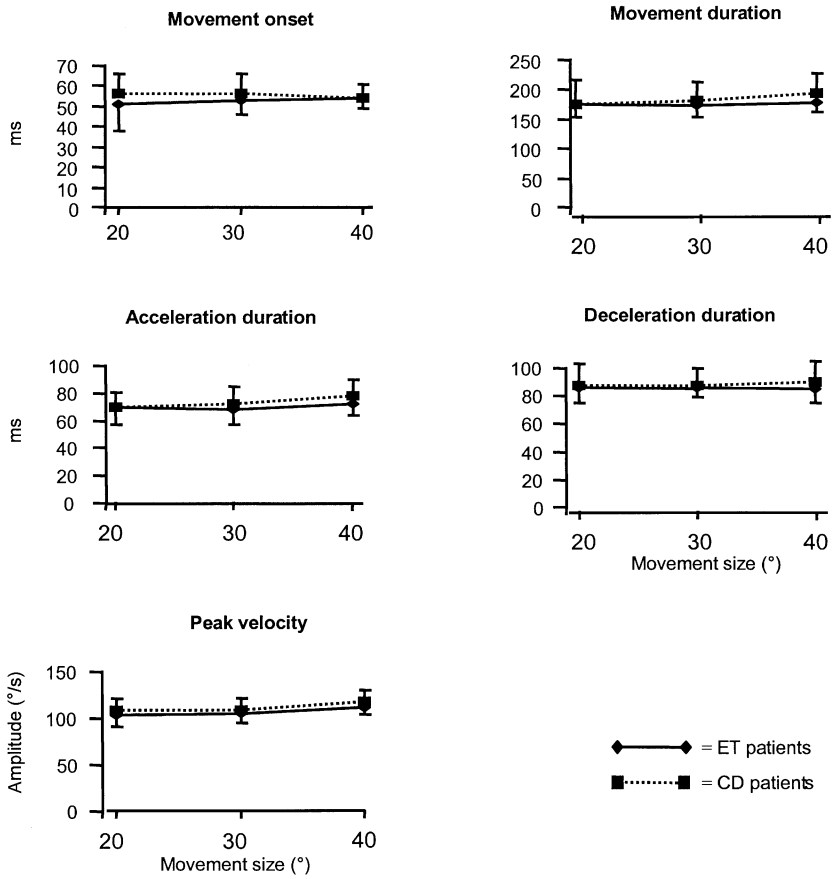

Fig. 3 Kinematic profile of ballistic wrist movements for the different movement sizes in ET and CD patients. There is no significant difference between ET and CD patients. Mean values are given. Error bars indicate 1 SD.

criterion. In the remaining patients, no consistent H reflex could be elicited.

Comparison between ET and CD patients

The grand average time course of RI in the two groups is shown in Fig. 5A, with the individual data from each patient superimposed in Fig. 5B. The mean size of the H-reflex response is expressed as a percentage of the control H-reflex size. There was no significant difference in the time course and depth of the early short-duration inhibition (repeated measures ANOVA, $P = 0.6$, interstimulus intervals of 1 and 0.5 ms median before radial nerve and 0.5, 1 and 2 ms radial before median nerve). This early inhibition is disynaptic, mediated via large group I afferents from the radial nerve and acts on median nerve alpha motor neurones through a single inhibitory interneurone (Day *et al.*, 1984; Rothwell *et al.*, 1988). The second phase of inhibition (interstimulus intervals of 10, 15 and 20 ms radial before median nerve), which reflects presynaptic inhibition of flexor Ia afferent terminals (Berardelli *et al.*, 1987; Rothwell *et al.*, 1988), also did not differ between ET and CD patients (repeated measures ANOVA, $P = 0.3$).

One difference between the groups that is apparent from examining the data in Fig. 5B is that there is much more intersubject variation in the level of presynaptic inhibition in CD than in ET patients. In ET patients, H reflexes were always inhibited to at least 80% of control values over intervals from 10 to 25 ms (mean of 60 ± 8% SD) (Fig. 5B), which is similar to healthy subjects (Day *et al.*, 1984). In contrast, this level of inhibition was present in only six of the CD patients. We therefore decided to subdivide the CD patients into two physiologically defined groups. One group (group A) consisted of the six patients with normal presynaptic inhibition (presynaptic inhibition $<80\%$ of the control H-reflex size at one or more time intervals). The other (group B) consisted of seven patients with abnormal presynaptic inhibition (presynaptic inhibition $>80\%$ of the control H-reflex size at all time intervals). The grand average data from these two groups are shown in Fig. 5C. Note that the SD of the results is now comparable with that of the ET patients.

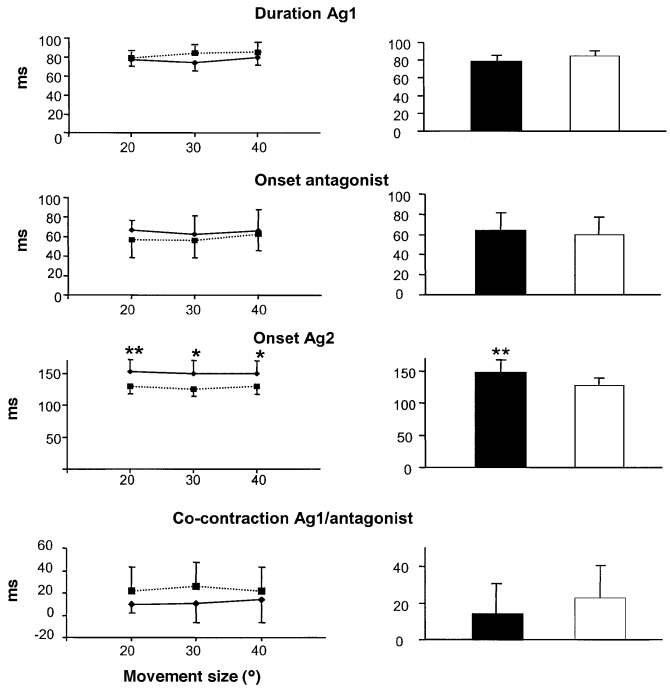

Fig. 4 EMG data of ballistic wrist movements of ET (continuous line and filled columns) and CD (dotted lines and open columns) patients. On the left side, mean values for each movement size are shown and on the right side mean values across all movement sizes (marginal means). Note that the onset of the second agonist burst (Ag2) is significantly later for each movement and also across all movement sizes in ET compared with CD patients. Repeated measures ANOVA with one between-subject factor (ET versus CD) and one within-subject factor (movement size) with three levels (20, 30 and 40°) showed a significant difference between subjects for onset of the second agonist burst [$F(1,23) = 15.7$, $P = 0.001$]. *Post hoc* independent samples *t*-test revealed significant differences between ET and CD patients for movement sizes of 20° ($t = 3.7$, $^{**}P = 0.001$), 30° ($t = 3$, $^{*}P = 0.013$) and 40° ($t = 2.8$, $^{*}P = 0.01$). Marginal means were also significantly different between the two groups ($t = 3$, $^{**}P = 0.005$). Ag1 = first agonist burst; error bars indicate 1 SD.

CD patients: 'dystonic' versus 'ET-like' arm tremor

The clinically defined subgroups ('dystonic' and 'ET-like') did not match those distinguished above on the basis of the amount of presynaptic inhibition (groups A and B). The grand average inhibition curves from 'dystonic' and 'ET-like' patient groups were very similar to the grand average of all CD patients (data not shown), and were not significantly different from those in the ET patients.

CD patients: normal RI (group A) versus abnormal RI (group B)

A posteriori, we explored the physiologically defined CD subgroups by analysing their demographic data (Table 2B). Whereas age, onset and duration of torticollis did not differ, onset age of arm tremor was significantly later and the duration of arm tremor significantly shorter in patients of group A. The distribution of onset ages of arm tremor and torticollis is shown for the two subgroups separately as well as combined in Fig. 6. In patients of group A, age of onset of both arm tremor and torticollis was widely distributed. In contrast, in patients of group B, arm tremor always started at or before the age of 20 years whereas there was a wide range of onset age for development of torticollis.

In individual patients of group A, duration of arm tremor was significantly correlated with duration of torticollis (Spearman rank-order correlation coefficient, $r = 0.883$, $P = 0.008$) but this was not the case in the patients of group B. This was because onset of torticollis and arm tremor was more or less simultaneous in the former group, but in the latter arm tremor started a mean of 20 years before onset of torticollis (Table 2B). There was no difference between other clinical features in the two subgroups (see Table 3) except for the fact that torticollis severity scores were significantly higher in patients of group A (mean TWSTRS score 16.3 ± 4 SD) as compared with those of group B (11.8 ± 3 SD, independent samples *t*-test, $P = 0.047$).

Ballistic wrist flexion movements in CD patients with normal RI (group A) and those with abnormal RI (group B)

Kinematic analysis did not show any significant difference between ET patients and the two CD subgroups (data not shown). However, EMG analysis showed that onset of the second agonist burst was significantly later in ET patients than in either of the two CD subgroups (independent samples *t*-test, $P = 0.03$ and $P = 0.04$, comparison of the onset of the second agonist burst across all movement sizes between ET patients and CD patients of group A and group B, respectively).

Since the difference between these CD subgroups lay in the effectiveness of RI, we focused our attention in the EMG analysis on the degree of co-contraction between first agonist and antagonist burst. There was a greater amount of co-contraction in CD patients in group B with abnormal RI (Fig. 7).

Discussion

The present data have shown that the EMG pattern that accompanies voluntary ballistic wrist movements in patients with classic ET differs from that in CD patients with arm tremor. This was true regardless of whether CD patients were classified on clinical grounds as having 'dystonic' tremor or 'ET-like' tremor. This suggests that the mechanism of arm tremor in CD might be different from that in ET.

RI data suggested that the CD patients with tremor could be divided into two subgroups, one with normal presynaptic RI (group A) and another with abnormal presynaptic RI (group B). These groups did not correspond to those based

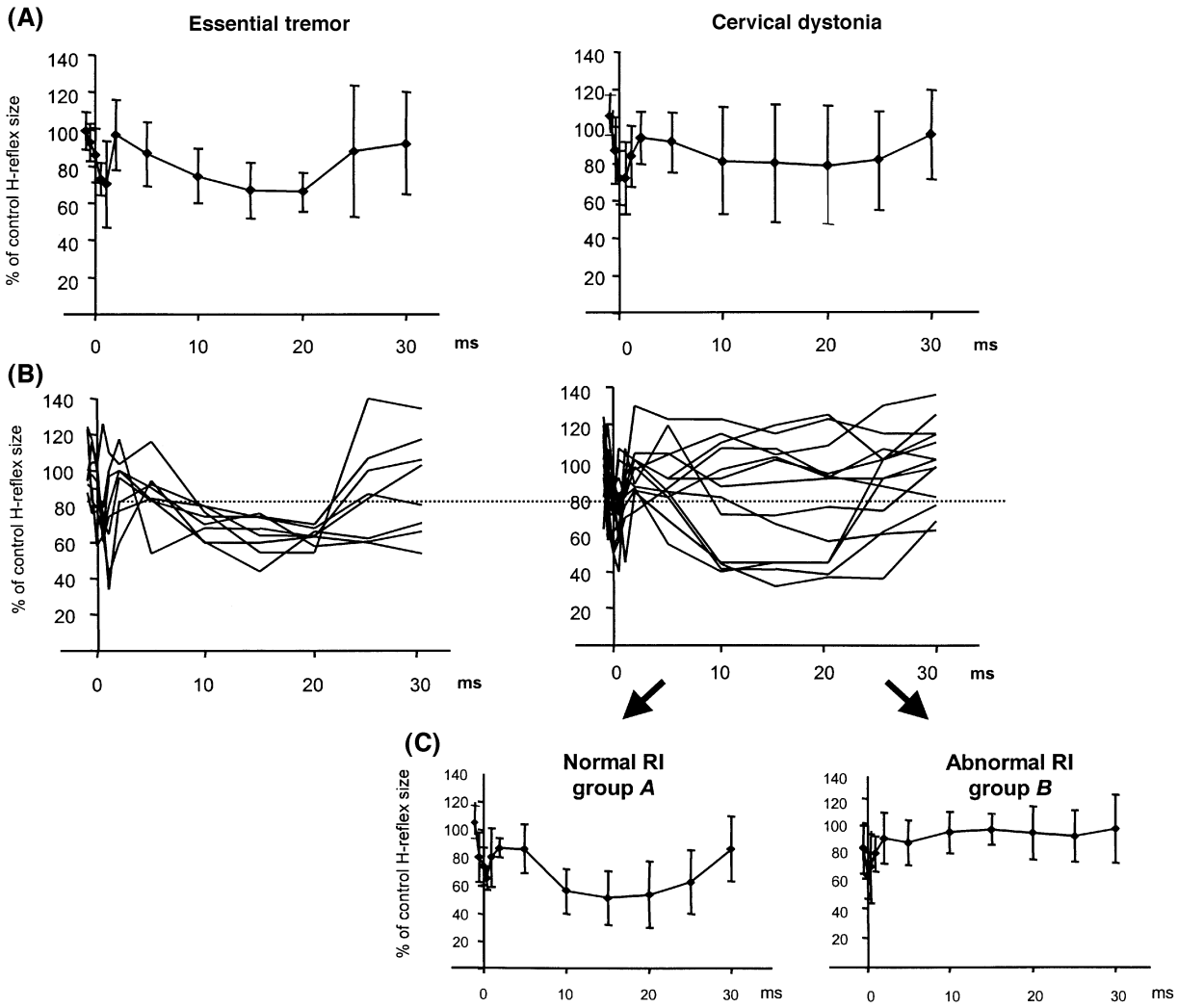

Fig. 5 Time course of the RI of the electrically elicited H reflex of a forearm flexor muscle in ET and CD patients. Inhibition at each time interval is expressed on the *y*-axis as a percentage of the size of the unconditioned H reflex. Error bars indicate 1 SD. (**A**) Grand averages of ET and CD patients ($n = 8$ and $n = 13$, respectively). (**B**) Superimposed individual H-reflex inhibition curves of ET and CD patients. Note that in all ET patients, the H-reflex size during the second (presynaptic) phase of inhibition was <80% (dotted line) of that of the control H reflex. This was the case in only six out of 13 CD patients. (**C**) Grand average of the electrophysiologically defined CD subgroups. Data of patients with normal RI findings (group A, $n = 6$) are shown on the left, that of patients with abnormal RI (group B, $n = 7$) on the right. In group A, mean H-reflex size at maximum presynaptic inhibition was 47 ± 14.3% SD (independent samples *t*-test, $P = 0.08$, comparison with ET patients), in group B it was 98 ± 14.9% SD ($P < 0.0001$, comparison with ET and CD patients with normal presynaptic inhibition).

on clinical tremor characteristics ('dystonic' versus 'ET-like' tremor). *A posteriori* analysis showed that these physiologically defined groups differed with respect to the age of onset of tremor and spread of symptoms. Ballistic wrist flexion movements also differed between CD patients of group A and those of group B, but not between CD patients with 'dystonic' and those with 'ET-like' tremor. This gives us more confidence in our proposed classification of CD patients on the basis of RI findings. If this grouping is correct, it has implications for the classification of these tremors and future genetic studies.

Ballistic wrist flexion movements

Ballistic wrist flexion movements have been studied extensively in different movement disorders including ET and dystonia (van der Kamp *et al.*, 1989; Britton *et al.*, 1994; see review by Berardelli *et al.*, 1996), but so far they have not been compared directly between ET and CD patients with postural arm tremor. Britton and colleagues found that the onset of the second agonist EMG burst was delayed in patients with ET compared with normal subjects (Britton *et al.*, 1994). They suggested that this was indicative of a cerebellar timing deficit that was directly related to the cause

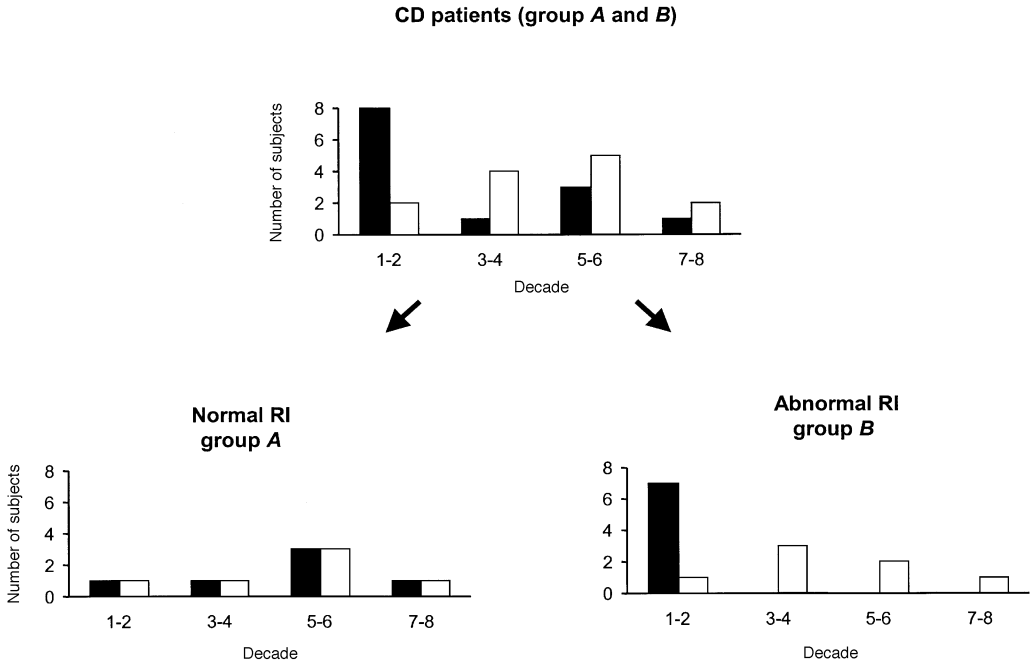

Fig. 6 Distribution of arm tremor and CD onset age in CD patients in whom H-reflex RI data were available (n = 13) (top). At the bottom, data of the subgroups with normal RI (group A) and abnormal RI (group B), respectively, are shown. Filled columns = onset of arm tremor; open columns = onset of CD.

of the clinical tremor. The present study showed that the onset of the second agonist EMG burst was not delayed in CD patients, and that this was true whether the CD patients had 'dystonic' or 'ET-like' tremor. It suggests that the underlying mechanism of the tremor in CD is different from that in ET.

RI findings in ET patients and CD patients with arm tremor

The present data showed that both pre- and postsynaptic mechanisms of reciprocal inhibition were intact in our group of ET patients. Similar results were reported by Rothwell in patients with wrist tremor and by Bain and colleagues in patients with writing tremor (Bain *et al.*, 1995; Rothwell, 1995). The results differ slightly from those in a recent paper by Mercuri and colleagues who reported that presynaptic inhibition in ET patients was reduced compared with normals, particularly in patients with the most disabling tremor (Mercuri *et al*., 1998). The reason for this discrepancy is not clear. As the clinical characteristics of their ET patients were not given, it is possible that they differed from those studied here.

The novel finding of the present data relates to the enhanced interindividual variability of presynaptic inhibition in our CD patients with arm tremor (Fig. 5B). As in ET, all CD patients had normal disynaptic inhibition, which is in accordance with previous data from this laboratory (Nakashima *et al*., 1989). Somewhat surprisingly, the level of presynaptic inhibition in our CD patients as a whole also did not differ significantly from that in ET patients, even though this inhibition was somewhat less pronounced. However, the range of presynaptic inhibition between patients in the CD group was much greater than that in the ET group. All ET patients had presynaptic inhibition of at least 80% of the control H-reflex size, whereas this was the case in only about half of the CD patients (group A) (Fig. 5B). In the remaining CD patients, presynaptic inhibition was absent (group B). This physiological division of the patients did not correspond to the clinical subdivision into 'dystonic' and 'ET-like' arm tremor. Nevertheless, it did lead to some surprising conclusions when we re-examined the clinical data, and was also supported by the data from the ballistic wrist movements (see below).

Comparison of CD patients with normal RI (group A) and those with abnormal RI (group B)

There were no obvious clinical features that distinguished patients of group A from those of group B (Table 3) at the time of study. There were a similar number of patients in each group with 'dystonic' or 'ET-like' arm tremor and there was no difference between the severity of arm tremor or the onset and duration of torticollis (Table 2B). However, *a posteriori* analysis showed that arm tremor always started before the age of 20 years in the patients of group B, whereas

Table 3 *Characteristics of arm tremor in CD patients grouped according to reciprocal inhibition findings*

Arm tremor characteristics	CD patients with normal RI (group A) (n = 6)	CD patients with abnormal RI (group B) (n = 7)
'Dystonic' arm tremor	3	4
'ET-like' arm tremor	3	3
Mainly up/down on posture	5	6
Mainly pro/supination on posture	1	1
Change from up/down to pro/supination on pro/supination movements	3	3
Additional kinetic tremor	5	6
Intention tremor	0	1
Position-specific deterioration	2	5
Asymmetric	5	3
Superimposed myoclonic jerks	3	1
Markedly irregular	4	4

CD = cervical dystonia; RI = reciprocal inhibition.

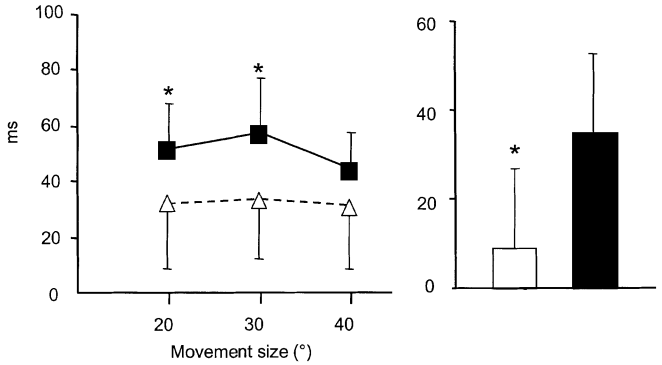

Fig. 7 Co-contraction of first agonist burst (Ag1) and antagonist burst during rapid ballistic wrist movements in CD patients. On the left side, mean values for each movement size are shown, and on the right side mean values across all movement sizes (marginal means). Error bars indicate 1 SD. Comparison between CD patients with normal RI (open triangles and column; group A, n = 6) and those with abnormal RI (filled squares and column; group B) (n = 17). The amount of co-contraction is larger in CD patients with abnormal RI (group B) [$F(1,11) = 5.16$; $P = 0.04$]. *Post hoc* independent samples t-tests revealed that the amount of co-contraction was significantly larger in patients of group B compared with those of group A for 20 and 30° movements (t = 2.3, $^*P = 0.04$; and t = 2.4, $^*P = 0.036$, respectively) but not for 40° movements. The mean values across all movement sizes also differed significantly (t = 2.3, $^*P = 0.04$, independent samples t-test).

there was a wide range of onset ages in patients of group A. Torticollis began in the fourth decade, at the usual age for adult onset primary focal dystonia, in both groups [Marsden, 1976, 1986; Chan *et al*., 1991; Epidemiological Study of Dystonia in Europe (ESDE) Collaborative Group, 1999]. The result was that in patients of group B, arm tremor occurred much earlier than torticollis. It is also interesting to note that at the time we studied them, patients in group B had usually had tremor for longer than those in group A, yet, despite this, the arm tremor at the time of this study was no more severe, and torticollis severity actually less, as compared with group A. Thus, the rate of progression of symptoms following onset was slower in patients of group B than in those of group A.

There is mention of similar patients in the literature. Rivest and Marsden described a group of three patients with early onset arm tremor (starting before the age of 15 years) and later spread of symptoms to the neck but not to the leg (Rivest and Marsden, 1990). In a clinical study of dystonia and arm tremor, Dubinsky and colleagues found that in all their CD patients with 'ET-like arm tremor', symptoms in the arms had preceded onset of symptoms in the neck by at least 5 years (Dubinsky *et al*., 1993).

In conclusion, our RI findings lead us to suggest that patients with CD and arm tremor may belong to one of two different groups, one with normal presynaptic inhibition between forearm muscles, in whom onset of arm tremor was late and simultaneous with onset of torticollis (group A), and another with deficient presynaptic RI, who had early onset arm tremor and later spread of symptoms to the neck (group B). This classification was supported when we re-examined the ballistic wrist movement data. Patients of group B had a greater amount of co-contraction between the first agonist and the antagonist bursts than those of group A. The division had not been evident when we compared the clinical groups of 'ET-like' and 'dystonic' tremor.

Significance of RI findings in CD patients with arm tremor

Reduced presynaptic inhibition between extensor and flexor muscles in the forearm has been described many times in patients with dystonia of the forearm and hand (Panizza *et al*., 1987, 1990; Nakashima *et al*., 1989). It may also be abnormal, although often to a lesser extent, in patients whose

dystonia affects other parts of the body whilst sparing the forearm (Deuschl *et al*., 1992; Chen *et al*., 1995), and can be abnormal in CD patients without arm tremor. Persistence of such subclinical abnormalities indicates that reduced presynaptic inhibition is not the cause of dystonic symptoms and tremor in the arm. Instead it might represent a predisposing factor, or an underlying 'dystonic trait', caused by an abnormal descending control of spinal inhibitory pathways. Perhaps abnormal presynaptic RI in the group of CD patients with early onset arm tremor (group B) is indicative of a 'more generalized' abnormality than seen in CD patients with later and simultaneous onset of tremor and torticollis (group A).

Tremor classification

Our study supports the current tremor classification that separates classic ET patients without dystonia from dystonia patients with 'dystonic' or 'ET-like' arm tremor (Deuschl *et al*., 1998). However, it also highlights a potential problem that could arise when classifying patients in group B. At onset, their tremor may resemble classic ET, yet they may not develop any signs of CD until many years later. It is therefore possible that some of these patients could be misclassified as classic ET if studied early in the course of their disease. In the absence of a positive family history, or if the family history data are inadequate, our findings indicate that it is impossible at presentation to decide whether a patient with arm tremor that fulfils the diagnostic criteria for ET indeed has classic ET or will instead eventually 'develop' into a dystonia patient. In the course of the disease, the rate of progression of symptoms may emerge as a distinguishing feature. ET usually progresses with age (Elbe *et al*., 1992). In contrast, on the basis of our study and reports of others (Deuschl *et al*., 1997), there appears to be little if any progression of arm tremor in CD patients, at least in those CD patients who have an early onset of arm tremor.

Conclusion

This study lends support to the view that classic ET patients should be classified separately from those patients who have arm tremor combined with dystonia elsewhere in the body. This is true whether the latter patients have 'dystonic' or 'ET-like' arm tremor. We have also found evidence for the existence of two distinct dystonia phenotypes that differ with respect to not only the results of electrophysiological tests but also the onset and progression of symptoms. Patients in group A had normal spinal presynaptic inhibition, and their arm tremor and CD started simultaneously around the age of 40 years. Patients in group B had reduced or absent presynaptic inhibition. Their arm tremor developed early in life (before the age of 20 years), up to 20 years before the appearance of cervical dystonia.

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