Essential Tremor and Senile Varieties of Action Tremor an Evolving ART

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Macdonald Critchley in his paper titled *'Observations on Essential (Heredofamilial) Tremor'* states that 'it is difficult to identify the first reference within the literature of the senile variety of essential tremor, for this type has certainly been noted as one of the hallmarks of old age for centuries'.[1] Critchley then notes that 'Trousseau (1885) mentioned that 'senile tremor' is not necessarily confined to old people and may appear in middle life or even adolescence, a conception which took many years to root itself within neurological teaching'. He then highlights the importance of the monograph 'Das Zittern' by J. Pelnár (1913) as being 'of importance in that it devoted no little space to a consideration of hereditary, essential and senile varieties [of tremor]' and works by Minor who noted the association of tremor, a large family size and longevity ('a status macrobioticus multiparus').[1] Critchley also addresses another interesting issue: 'Although popularly regarded as a characteristic manifestation of senility, it must be remembered that tremor is actually an uncommon physical sign in old age' and quotes his own paper (Critchley 1931) as well as citing observations by Charcot (1876, 1887) in support of this view.[1 2]

Critchley's contribution is most helpful in setting up two interesting questions: Is 'senile tremor' a different entity to essential tremor (ET) or just a (late onset) variant of essential tremor? And, does essential tremor confer increased longevity, compared to a normal population?

Deuschl and colleagues grapple with these questions using the resources of the 2001 cohort of The Longitudinal Study of Aging Danish Twins (LSADT), which invited all twins aged $\geq$ 70 years old in Denmark to participate, and involved face to face interviews of the participants by trained lay personnel.[3] Medication and mortality data were available and all subjects were followed for 11 years. By 1st January 2013 1,532 (63.8%) of the participants had died. 2,448 people from the LSADT (2001 cohort) answered a seven item screening questionnaire for ET. Following the exclusion of people with self reported Parkinson's disease or on anti-Parkinsonian medication, a group of 2,056 (84%) of them drew Archimedes spirals, to measure tremor severity using the Bain & Findley 0-10 Scale, and had their grip strength, cognitive function (5 cognitive test battery) and activities of daily living (11-item ADL questionnaire) assessed as markers of a 'classical aging phenotype'.[3 4] Of this

cohort 25.5% had 'clinically visible tremor' (using a spiral score > 3 as a surrogate marker) and 222 screened positive for ET.[3]

Of these a subgroup of 276 underwent examination by a movement disorder neurologist, of whom 128 had no tremor (controls), 105 had ET (36 definite, 69 probable or possible by TRIG criteria) and 43 were excluded because they had other causes of tremor, including 14 with PD.[3]

Data from the large (n=2,056) screened cohort showed that the spiral score significantly increased with age and tremor severity. Thus the percentage of people afflicted by tremor (spiral score > 3) increased from about 25% of those in their 8th decade to 50% by the 10th decade.[3] There are three possible explanations for this finding:

1. A late onset' action tremor develops in some elderly people, increasing the proportion of tremulous people by 25% between the 8th and 10th decade.
2. People with tremor (spiral scores > 3) are more likely to survive than elderly people with little or no tremor, increasing the proportion of tremulous people in older cohorts.
3. Being a cohort study it is possible that the older people in this study were subject to an environmental cause of tremor in their youth that had less effect on the younger elderly people in the cohort, or there may have been changes in the genetic makeup of Danish Twins between 1901 and 1931 that decreased the risk of tremor emerging in later life.

The study by Deuschl and colleagues provides an answer to this issue as an increased spiral score was significantly correlated with increased mortality and lower physical indices (grip strength and ADL scores) and cognitive function. Indicating that tremor in people aged 70 or over is associated with an *increase* in morbidity and mortality. Furthermore, multivariate analyses demonstrated that an increased spiral score was an independent risk factor for mortality.[3] This has an important implication, which is that the increasing prevalence of tremor from the 8th to the 10th decade is likely to be the result of new incident tremor cases. This tremor is often of late onset and is an action tremor that affects the upper limb(s) (as evident in spirals). It might also affect other parts of the body too but whether or not this is

the case is not known. It seems unlikely that a gradual tremorgenic environmental or genetic change to the Danish population occurred many decades previously that could explain the progressively increasing prevalence of tremor with age over 70 years.

Data from the 36 definite ET cases identified in the subgroup of 276 people who underwent neurological examination showed that, compared to the 1913 controls in the large cohort, the definite ET cases had significantly *better* ADL and cognitive scores and a non-significant trend towards *decreased* mortality. However, this apparent positive effect of ET on physical and cognitive function was not found for grip strength and not for the probable and possible ET cases. Even so, it is noteworthy that the definite ET cases did not have an increased morbidity or mortality.[3]

The key tool used in this study and upon which conclusions are based is the Archimedes spiral. The use of a 0-10 scale to score spirals as a way of assessing tremor severity was first shown to be reliable and valid by Bain et al. in 1993, a view which has been confirmed by the MDS Task Force Report on scales for screening and evaluating tremor, who recommend the use of spiral scores for evaluating essential tremor.[4-6] Consequently, the use of spirals in this study seems robust. Although the use of spirals to assess tremor severity is routine and spirals have also been shown to be useful for differentiating ET from PD, Deuschl and colleagues discover a remarkable fact, namely that the (0-10) spiral score correlates with mortality and also physical and cognitive morbidity in elderly people.[3 7] Why this should be the case is not clear, as the causes of death in the cohort were not documented.

So what is/are the cause(s) of this upper limb action tremor in these elderly people which confers increased morbidity and mortality? Could it be some form of physiological tremor enhanced by age? The answer is probably not because the amplitude of physiological tremor is not increased in the elderly, although tremor frequency does decline slightly.[8] Intriguingly, postural physiological tremor regularity and tremor-EMG coherence are increased in the elderly but this does not account for Deuschl and colleagues findings.[8] It is unlikely to be hereditary essential tremor as this is fully penetrant by 65 years and has a bimodal age of onset with peaks in the 2nd and 6th decade or the result of dystonic tremor syndromes, which

also have a bimodal age of onset, with 90% of dystonia associated tremor manifest by 60 and 90% of dystonic tremor by 70 years of age [Figure]. [910] However, this does not rule out the possibility of a late onset variant of sporadic essential tremor, previously referred to as 'senile tremor' by J. Pelnár in 1913 being the culprit.[11] However, although it is tempting to conclude that this entity is just a late onset variant of sporadic essential tremor, the apparent differences in morbidity and mortality associated with this 'age related tremor' compared to elderly people with definite ET indicate that it has a different prognosis, which in turn suggests that it is a different entity to ET.[3]

In terms of nomenclature Deuschl et al. invoke the term 'age related tremor' (ART) for tremor apparent at 70 and over, in order to distinguish it from essential tremor.[3] However, many types of action tremor commencing at a younger age continue to manifest in old age. Consequently, this term is confusing as it combines tremors that persist into old age and those first appearing in old age. The phrase 'the senile variety of tremor' coined by Pelnár has the same issue, although its cognitive inferences, are not necessarily inappropriate given the association of this tremor with lower cognitive function detected by Deuschl and colleagues.[3] [11] Thus the terms 'age related tremor' or 'senile variant of tremor' are somewhat ambiguous.

Deuschl and colleagues construct a hypothetical model (see Figure 3 in their paper) showing, that because there is a marked increase in the prevalence of tremor with older age and that because the incidence of ET decreases after the 7th decade, there must be a late onset type of pathological tremor to account for this increase. [3] [12] The main characteristics of this type of tremor, are:

1. It is an action tremor which is evident in spirals. [However, it is not known whether or not there is also a rest component (at least in some cases) because this would not be reflected in a spiral].
2. It affects the dominant upper limb, although it may well also involve the non-dominant arm and other parts of the body.
3. It has an increasing prevalence over the age of 70 years but does not affect the majority of elderly people over 70 years old.
4. It has an increasing severity with age over 70 years.

5. It is associated with a worse than normal prognosis.

Perhaps ‘late onset upper limb action tremor’, although cumbersome, is a more accurate description of this form of tremor and is preferable to ‘age related tremor’, ‘senile variety of tremor’ or ‘senile tremor’, although the entity of ‘late onset action tremor’ must be inferred from the results of the study. The cause of this type of tremor is unknown, although it is unlikely to be physiological tremor. It does not appear to be related to medication and there is no data to suggest that it is related to cumulative alcohol consumption.[3] No neurophysiology and imaging studies were undertaken on *these* elderly tremulous people and it is also possible that ‘late onset action tremor’ may have several causes.

In an attempt to address this issue Muthuraman and colleagues conducted a pathophysiological study, comparing 20 patients with young onset essential tremor (yo-ET; mean age of onset ~7 years old) and 10 with middle age of onset ‘age related tremor’ (mo-ART; mean age of onset of 57.9 years, coincident with the second peak of onset in previous studies of ET).[9] The mean age of these mo-ART cases was 69.7 years, different to the Danish Twin Study in whom *all* subjects were $\geq$ 70 years old, so that considerable caution is required in extrapolating results between the studies.[3 13] Nevertheless, the results showed that for the mo-ART group the maximal coherence, between EEG and surface EMG, was significantly less than in the yo-ET group. In addition source analysis indicated that the circuitry may be different, as a cortico-brainstem-cerebello-thalamo-cortical network was apparent in yo-ET, whereas only a cortico-thalamic network was revealed in the mo-ART group. Intriguingly, there were similar differences in the ‘aging parameters’ between the mo-ART and yo-ET groups to those found between the ET and ART groups in the Danish Twin Study, suggesting that extrapolation between the two studies’ populations might be reasonable.[3 13] However, a confounding factor in Muthuraman and colleagues study was the duration of tremor (about 45 years longer in the yo-ET than mo-ART group).[13]

Consequently, data from longitudinal, clinical and pathophysiological, studies are awaited to more accurately characterize the entity of late onset upper limb action tremor so that the MDS Task Force on Tremor can then consider providing an appropriate name and definition

to this entity, particularly as the distinction from ET may have important therapeutic implications.

Finally, the finding that the 0-10 score in a simple spiral is an independent risk factor for mortality amongst elderly people is fascinating.[3]

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Legend to Figure:

Distributions of ages of tremor onset for 95 patients with dystonic tremor syndromes (DTS). DT: Dystonic tremor; TAD: Tremor associated with dystonia; DT & TAD: patients with both DT & TAD.