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Re-emergent Tremor: What do we know so Far?

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Re-emergent Tremor (RET) is defined as a tremor of the upper limbs that appears after a varying latency during a posture. Although RET was first described almost 20 years ago [1], few studies have investigated the clinical features of RET.

In 1999, Jankovic et al., first described RET in a small sample of patients affected by Parkinson's Disease (PD). The authors observed that PD patients with rest tremor may show a postural tremor starting after a variable delay while maintaining the upper limbs outstretched [1]. Given that RET and resting tremor showed similar clinical features,Jankovic et al., hypothesized that RET depends on the activity of the central oscillators responsible for resting tremor that is reset with some latency after the assumption of a new posture. In the same study, Jankovic et al., also observed that patients with essential tremor never showed RET, thus suggesting that RET was specific to PD. This hypothesis was supported by Schwingenschuh et al., [2] who compared upper limb tremor in patients with PD and patients with "Scans Without Evidence of Dopaminergic Deficit" (SWEDD) and reported that only patients with PD had RET. No studies have detected RET in patients with atypical parkinsonisms or dystonic tremor. By contrast, De Laat et al.,[3] described a SWEDD patient who had RET.The presence of RET, therefore, seems to be strongly suggestive of PD but RET should be always assessed in patients with tremor syndromes.

Only two studies have investigated the occurrence of RET in PD. The first, in which the aim was to evaluate occurrence and the clinical features of action tremor[4], showed that RET was present in 32% (63/197) of patients with PD. A second study [5] specifically designed to investigate RET in PD reported that 20% (42/210) of patients have RET. In the first study, the authors [4] did not, however, specify whether PD patients were evaluated while they were off or on pharmacological treatment. In the second study [5] instead, only PD patients who were on their usual therapeutic regimen were studied, which means any effect of pharmacological treatment on RET was not evaluated. In this regard, unpublished investigations from our group on the presence of RET in PD patients who were evaluated both off and on treatment showed that RET was more frequent when patients were evaluated off treatment.

In PD, RET usually involves the upper limbs [1,4-6] and is bilateral in 50% of cases [5]. Recent clinical reports have described patients with PD with RET even in the jaw [7] and tongue [8,9]. No studies have yet reported RET in the lower limbs, though this may be due to the fact that the investigation of postural tremor in the lower limbs is not a common clinical procedure.

RET is considered as a clinical variant of resting tremor. The clinical features of patients with RET and patients with isolated resting tremor have been compared in two different studies [5,10]. Both studies showed that the two groups of patients, who were on an equivalent mean levodopa dose, did not differ significantly in age at disease onset, disease duration or severity. Furthermore, Belvisi et al.,[5] observed that the severity of non-motor symptoms was also similar in the two groups of patients. Previous accelerometric [1,11] and electromyographic recordings [12] have shown that both the frequency (about 4.5-5.5 Hz) and the asynchronous pattern of antagonistic muscle activation [6,12] are similar in RET and resting tremor. The severity of RET positively correlates with that of resting tremor in PD patients on treatment [5]. Moreover, patients with bilateral RET tend to display bilateral resting tremor, while patients with unilateral RET may display unilateral resting tremor alone [5]. Overall, these findings support the hypothesis that RET is a variant of resting tremor. A number of structural [12], diffusion tensor [13] and functional [14,15] Magnetic Resonance Imaging (MRI) studies have investigated resting tremor networks in

PD. Similarly, several neurophysiological techniques, including transcranial magnetic stimulation [16-19] and local field potentials recording [12,20-23], have been used to investigate the pathophysiology of parkinsonian resting tremor. Future MRI and neurophysiological studies are needed to confirm if the same brain circuits underlie RET and resting tremor.

By comparing patients with RET and patients with resting tremor associated with action tremor, Belvisi et al.,[5] observed that PD patients with RET on treatment had milder speech, posture and gait disorders and milder upper limb and global bradykinesia than patients with resting tremor associated with action tremor, which suggests that patients with RET represent a benign subtype of PD. The differences between the clinical features of patients with RET and of those with action tremor may reflect different pathophysiological mechanisms. Indeed, previous studies have suggested that the presence of action tremor implies a greater involvement of non-dopaminergic systems in PD, including the cerebellar [17,19] and serotoninergic systems [24]. However, it should be borne in mind that no studies have yet investigated the pathophysiology of RET by comparing patients with RET and those with action tremor.

One important feature of RET is the latency between the assumption of the posture and the start of tremor. It has been suggested that the latency between resting tremor and RET may reflect a transitory inhibition of the central nervous system tremor generator induced by the proprioceptive feedback generated by the repositioning of the limbs from rest to outstretched.In keeping with this hypothesis, different studies have reported a mean latency of RET of 9 seconds [1,4,11] with patients displaying a comparable latency between the right and left sides when RET is bilateral [5].

RET is always associated with resting tremor. Exceptions to this rule are the description of one patient with PD without resting tremor who displayed postural tremor after latency of 1-7 seconds [25] and of another patient with Moyamoya disease following infarctions in the lenticular nucleus [26].

To conclude, RET is a relatively common disorder in PD and patients with RET may represent a benign subtype of this disease, even within the tremor-dominant phenotype of PD. Future neurophysiological and neuroimaging studies are warranted to shed more light on the mechanisms underlying RET and its relationship with resting tremor in PD.

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