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Movement disorders

Current concepts of essential tremor

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ABSTRACT

Essential tremor is clinically defined but there is increasing evidence that it is not a unique entity. Its pathophysiology has been studied with many methods but may also vary between subtypes. Neurophysiologically, there is strong evidence that a specific cerebello-thalamo-cortical loop is abnormally oscillating. The cause of its uncontrolled oscillation is not yet understood. The clear proof of a degenerative cause is still lacking and abnormal receptors or other causes of altered non-progressive functional disturbance cannot be excluded. Strong evidence supports the major involvement of the cerebellum and there is ample evidence that GABA is the main neurotransmitter involved in the pathophysiology in ET. Genetics have provided so far only a few rare subtypes which are due to specific mutations but there is no doubt that it is mostly a hereditary condition. There is evidence that the large subgroup of late onset tremor is a separate condition and this tremor is an independent risk factor for earlier mortality and comes with signs of premature aging (aging-related tremor). It will be important to improve phenotyping of patients in more detail possibly to include not only features of the tremor itself but also other clinical assessments like force measurements or cognitive testing. Based on these variables, we may be able to better understand the presumably different mechanisms underlying different variants of the disease.

1. Introduction

Essential tremor is the most common movement disorder affecting approximately 1% of the general population and about 5% of the population over 65 years [1]. Clinically, ET is characterized by a progressive symmetrical postural and kinetic tremor of the upper limbs in the absence of other neurological deficits. However, the term ET encompasses a wide range of heterogeneous clinical phenotypes and apart from tremor symptoms suggestive of cerebellar dysfunction and presence of non-motor symptoms like cognitive impairments may be seen in ET patients as well [2–6]. Despite its high prevalence, the underlying pathophysiology of essential tremor is poorly understood. Given the presumed clinical heterogeneity, we cannot exclude that there are even different pathophysiological mechanisms active in different variants of ET. Nevertheless, the conclusive effect of thalamic deep brain stimulation and the fact that lesions anywhere in the cerebello-thalmo-cortical network might alleviate tremor, prompted the hypothesis of essential tremor as an ''oscillating network'' disorder [7,8]. Although the involvement of the cerebello-thalamo-cortical network and in particular the cerebellum became increasingly

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evident, the source of oscillatory activity remains largely unknown [9,10].

The aim of this article is to summarize the current pathophysiological concepts of essential tremor and to emphasize the pros and cons of current hypotheses regarding this condition.

2. The heterogeneity of essential tremor

According to the MDS consensus statement on tremor ET is defined as a bilateral, largely symmetrical, postural or kinetic tremor affecting hands and forearms that is visible and persistent in the absence of other neurological signs in particular dystonia [11]. Although this classification has been a benchmark in the field of tremor, advances over the past decade highlighted several caveats. Notably it became increasingly evident that even under strict adherence to the consensus criteria ET is a clinical heterogeneous entity [12]. Further aggravating factors that increase heterogeneity is first the circumstance that many have expanded the phenotype of ET to include subtle cerebellar abnormalities [13], cognitive deficits [14], etc. and secondly that it is common for investigators to deviate from the MDS criteria [15]. Respectively, it is certainly not surprising that heterogeneity is not only restricted to the clinical presentation but it is seen in multiple domains including ET pathophysiology. In particular, the lack of biomarkers and a post-mortem gold standard like the presence of Lewy bodies in the substantia nigra in PD patients is a continuous problem bearing in mind the high misdiagnosis rate of ET [16].

The assumed heterogeneity in ET patients is necessarily not captured in the current criteria and was not adequately considered in most pathophysiology studies in the past which possibly gives rise to conflicting results between essential tremor studies. Accordingly, a new tremor classification scheme is needed which captures this heterogeneity to avoid further confusion in the literature.

3. The oscillating network hypothesis

Since the turn of the century, it is known that ET is associated with increased activity in the cerebello-thalamo-cortical circuit although the source of oscillatory activity is still ambiguous [17]. Neurons in the thalamus, inferior olive, and possibly the cerebellum have unique electrical properties allowing them to oscillate independently at a given frequency [18,19]. Accordingly, tremor research in the past was focused to localize single oscillators. However, in recent years accumulating evidence exists that this is not the case. Lesions, which are known to ''cure'' tremor in ET lie within the cerebello-thalamo-cortical circuit, which supports the hypothesis that this network is, activated already relatively downstream the cascade of events causing tremor. Interestingly, in contrast to the thalamus, cortex, pons or cerebellum lesions in the inferior olive have so far not been reported to result in tremor improvement. Traditionally, the inferior olive-cerebellar network has been regarded as a probable pacemaker feeding into the tremor circuit in essential tremor patients. The bulk of evidence in favor of the critical role of the inferior olive comes from animal data [20] and apart from a PET study performed by Hallett et al., which showed possible abnormality of the inferior olivary nucleus [21] the evidence for a malfunction of the inferior olive in humans is poor. A further point, which argues against a single oscillator, is the fact that corticomuscular coherence in ET may lose intermittently without observing any changes in peripheral tremor activity [22]. While in earlier days the argument of a single oscillator has been put forward recent studies have meanwhile demonstrated that for ET there is no coherence between the trembling muscles of different extremities and therefore a common oscillator for them is unlikely [23,24]. Additionally, DBS studies in ET patients and tremor-dominant PD have shown that multiple, spatially separated tremor clusters in the thalamus are involved in the generation of tremor [25]. Accordingly, the attention of tremor research shifted from single oscillator regions in the brain towards network dynamics within the cerebello-thalamo-cortical network, such as the strength and directionality of interregional connectivity.

Buijink et al. recently demonstrated via effective connectivity analysis a significant excitatory modulating effect of tremor variation on the extrinsic cerebello-dentato-thalamic connection and the intrinsic activity of the thalamus and the cerebellar lobule V [26]. Similar like previous studies they found decreased cerebello-cortical functional connectivity related to a motor task. Interestingly, decreased functional coupling between the primary motor cortex and posterior cerebellum was associated with an increase in tremor severity. Additionally increase in tremor severity was associated with increased functional connectivity between cerebellar lobule I-IV and the motor thalamus. These results support the idea of pathological entrainment within the cerebellar thalamic system. Interestingly, an EEG-EMG study performed by Raethjen et al. demonstrated an intermittent cortical involvement suggesting that cortical involvement is not a crucial player in the tremor network [22]. A possible explanation might be that perturbed cerebellar output generates improper thalamic activity, which disrupts physiological motor related connectivity with the motor cortex [19,27]. The results by Buijink et al. support the hypothesis that increasing tremor severity proportionally disrupts cerebello-cortical connectivity. Further, continuous increased input from the dentate nucleus via the thalamus might cause amplification of inhibitory mechanisms within the cerebral cortex.

Apart from tremor cognitive functions including attention, working memory, visuospatial, executive functions and emotions were found to be impaired in ET patients [6]. The underlying pathophysiology of cognitive impairment remains largely unknown and only few studies explicitly investigated this topic. Cognitive sequelae as a consequence of cerebellar dysfunction are well known [28,29]. Troester et al. [30] hypothesized that the cerebello-frontal loop might be affected by the disturbance of cerebellar functions induced by the oscillating neurons in the cerebellum due to tremor. Passamonti et al. demonstrated in a fMRI study that connections between the cerebellar posterior lobules, dorsolateral prefrontal cortex and parietal lobules were altered during a verbal