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Studying cerebellar dysfunction in neuropathy-related tremor

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Tremors may occur in the setting of peripheral neuropathy; however, the pathophysiology of neuropathy-related tremors remains poorly understood. A compensatory mechanism in the central nervous system, in response to peripheral neuropathy, has been postulated as a mechanism for such tremor generation. Among the central oscillatory structures, the cerebellum has been postulated to be involved in a range of tremor disorders, including essential tremor (ET), Parkinson's disease (PD), "cerebellar tremor", and Holmes tremor (Elble, 2009). With this in mind, Saifee et al. conducted a study of cerebellar physiology in a group of patients with genetically-confirmed Charcot-Marie-Tooth (CMT) disease (Saifee et al., 2015). The authors found that CMT patients with tremor and those without tremor did not differ in terms of visuomotor adaptation or classical eyeblink conditioning, which are two classical cerebellar tasks. In addition, CMT patients with tremor did not have spontaneous or gaze-evoked nystagmus and had normal pursuit and saccadic eye movements. Based on these observations, they concluded the likely presence of normal cerebellar function in CMT patients with tremor.

This report is interesting in that it investigates the role of the cerebellum in CMT tremor and highlights that CMT patients with tremor differ from ET patients, as eyeblink conditioning has been reported to be abnormal in ET (Kronenbuerger et al., 2007). Cerebellar involvement in ET has been further supported by brain functional magnetic resonance imaging studies (Sharifi et al., 2014) and postmortem studies (Louis, 2014). ET patients often also have a number of subtle cerebellar signs such as impaired tandem gait (Rao et al., 2011). Similarly, cerebellar involvement is well-documented in patients with dystonia in neuroimaging studies, and eyeblink conditioning has been found to be abnormal in patients with dystonia (Sadnicka et al., 2012). Therefore, eyeblink conditioning is a useful tool to probe the differential role of the cerebellum in a range of movement disorders.

However, the current study also requires cautious interpretation. The sample size was quite modest, raising some question about the ability to broadly generalize from these results.

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Also, a control group was not included for all clinical and physiological measurements. Furthermore, the lack of the observed deficits in eyeblink conditioning and visuomotor adaptation in this small sample does not completely rule out cerebellar involvement in CMT patients with tremor. Although wide-spread areas of the cerebellum are activated during eyeblink conditioning (Cheng et al., 2014), it is still possible that cerebellar involvement in CMT patients with tremor lies outside of these regions. Another possibility is that the cerebellum in CMT patients with tremor is not dysfunctional; rather, the normal cerebellum reacts to abnormal spinocerebellar inputs, which leads to tremor generation. This concept that tremor can be generated by the cerebellar circuitry in response to defects in other brain regions has been implicated in PD tremor. PD tremor originates in the basal ganglia but the cerebellum plays an important role in tremor augmentation and modulation (Wu and Hallett, 2013). Yet, PD patients have intact eyeblink conditioning (Sommer et al., 1999). To put the current findings into context, patients with PD or CMT tremor do not have eyeblink conditioning defects, which is different from ET patients. Perhaps tremor in PD and CMT results from deleterious compensatory mechanisms of central oscillatory structures (e.g., the cerebellum) in response to the primary defects (basal ganglia in PD and peripheral neuropathy in CMT disease). On the other hand, ET might be a primary cerebellar disorder. This notion derives some support from the recent findings of structural changes in the cerebellum in postmortem studies of ET patients, including the presence of Purkinje cell axonal pathology (Babij et al., 2013) and abnormal climbing fiber-Purkinje cell connections (Lin et al., 2014).

Interestingly, CMT patients with tremor and those without tremor did not differ in terms of their median nerve conduction velocities and *F*-wave latencies. However, the mean size of the compound muscle action potentials (CMAPs) seemed to be smaller in the non-tremulous patients than that in the tremulous patients, although not statistically significant. A larger sample size study will be required to determine whether the size of CMAPs differs significantly in these two groups. Understanding the relationship between CMAPs and tremor is important, as the size of CMAPs is a strong indicator of disability in CMT patients (Kim et al., 2012). In addition, weight loading did not change the tremor frequency, which suggests a central mechanism. However, how and when these central oscillatory structures are activated to generate tremor secondary to neuropathy remains to be investigated.

CMT is a group of heterogeneous diseases with different degrees of demyelination and axonal pathology, which might add to the diversity of mechanisms of tremor generation. In addition, genetic mutations that cause CMT might broadly affect the central nervous system in addition to the peripheral nervous system. For example, *pale tremor* mice with the *CMT4J* mutation, which have severe tremor, exhibit degeneration of sensory and autonomic ganglia and also neuronal loss in the cerebellar nuclei, thalamus, pons, and medulla. These abnormal central structures along with peripheral neuropathy can lead to tremor generation (Chow et al., 2007). The current study focuses mainly on CMT1A and CMT1B patients; therefore, the findings may not be generalizable to tremors in all CMT patients or to tremors in patients with other forms of peripheral neuropathy (Said et al., 1982).

Moreover, peripheral neuropathy-related tremor can also have diverse clinical presentations: ET-like tremor, enhanced physiological-like tremor, or cerebellar tremor; the causes of each

tremor type might differ (Elble, 2009). For example, in inflammatory neuropathy-associated tremor, there is significant impairment in eyeblink conditioning, suggesting abnormal cerebellar function (Schwingenschuh et al., 2013). Therefore, it would be helpful to study a large group of patients with tremor and peripheral neuropathy and to stratify patients based on tremor characteristics. Additional control groups, including patients with cerebellar ataxias, ET, and PD, would also be helpful in order to delineate the degree of functional cerebellar impairment in ET and cerebellar ataxia as compared to controls, PD, and patients with CMT tremor.

Recent research has put the cerebellum at the center stage in discussions of the circuitry involved in various tremors. Different tremor presentations might involve distinct cerebellar circuitry or might result from diverse synaptic plasticity within the circuitry. Future studies of peripheral neuropathy-related tremor will need to focus on functional neuroimaging to definitively conclude whether the cerebellum is involved or not. The postmortem examination of the CMT cerebellum will also provide information. Eventually, the role of cerebellar circuitry in CMT tremor might be studied in animal models of CMT with tremor. Knowing whether procedures to disrupt cerebellar circuitry would dampen the tremor in these CMT animal models will further our mechanistic understanding of this entity. The study under discussion adds one more piece to a complex puzzle.

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