Pathophysiology of Nonparkinsonian Tremors

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Abstract: Patients with nonparkinsonian tremors are the second largest group treated with functional neurosurgery. We summarize the present pathophysiological knowledge of these conditions. Essential tremor (ET) may be due to oscillations within the olivocerebellar circuit. There is experimental evidence from animal models for such a mechanism, and clinical data indicate an abnormal function of the cerebellum in ET. Cerebellar tremor may be closely related to the tremor seen in advanced ET. The malfunction of the cerebellum causes a pathological feed-forward control. Additionally an oscillator within the cerebellum or its input/output pathways may cause cerebellar tremor. Almost nothing is known about the pathophysiology of dystonic tremor. Holmes tremor is based on a nigral and a cerebellar malfunction and presents clinically as the combination of tremor in Parkinson’s disease and cerebellar tremor. Neuropathic tremor can be extremely disabling and is thought to be due to an abnormal interaction of the disturbances within the periphery and abnormal cerebellar feedback. Unlike the case of Parkinson’s disease, functional neurosurgery of nonparkinsonian tremors is not yet based on a solid pathophysiological background. © 2002 Movement Disorder Society

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In the case of Parkinson’s disease, new pathophysiological insights have significantly influenced the targets for functional stereotactic surgery, both for thermocoagulation and for deep brain stimulation. Without recent knowledge of the basal ganglia circuits and their abnormal functioning, the subthalamic nucleus would not have been used as the target for surgery. For tremors other than parkinsonian tremor, our understanding is much less advanced. Despite a long neurosurgical tradition of treating them with lesions of the thalamic ventralis intermedius (Vim) or the zona incerta our understanding of their pathophysiology is poor. This overview has selected those issues which a basic neuroscientist and a clinician, both specialized for movement disorders, consider to be of potential importance for a future integrative pathophysiology. Tremors are based on one of four basic pathophysiological principles: mechanical oscillations, reflex oscillations, central oscillations, or a feedback-driven oscillation. These principles often interact in a particular tremor but mostly one of these mechanisms is dominant. Almost all tremors that may be considered for functional neurosurgery are due to central oscillations or another central mechanism. In our view, the following tremors either represent an established indication or may improve with functional neurosurgery essential tremor, parkinsonian tremor, dystonic tremor, cerebellar tremor, Holmes tremor, or neuropathic tremor. Parkinsonian tremor is dealt with in a parallel study and is for that reason not specially mentioned here. The present study is partly based on a recent review.

ESSENTIAL TREMOR

Essential tremor is a mostly hereditary condition, and linkage has been found for several genes. Pathoanatomical investigations could not yet identify any morphological changes. This finding supports the idea that ET is due to a functional abnormality within the central nervous system (CNS). Clinically, it is a slowly progressive, monosymptomatic disorder with postural and kinetic tremor; in advanced stages, intention tremor can severely handicap the patients affected.

Different lines of evidence support the hypothesis that essential tremor is caused by a functional disturbance of
the olivocerebellar circuit. The most convincing clinical evidence is probably the observation that ET disappears after lesions of the cerebellum, the pons, or the thalamus; locations which are all part of the cerebrocerebellar loop. Positron emission tomography (PET) studies have shown that there is cerebellar hyperactivity in ET, although it is not yet clear whether this is the cause or the result of tremor in ET. Harmine, a β-carboline related to harmaline has been shown to induce a tremor in normal man, which shares some features with ET. Therefore, the animal studies with the harmaline model of tremor are of specific interest for the pathophysiology of ET. It could be shown for different species, that cells of the inferior olive get synchronized and that their rhythmic activity is transferred through the cerebellum and the reticulospinal projections to the motoneurons. The hypothesis has been put forward that ET could be generated in a similar way.

A recent line of evidence comes from the study of cerebellar functions in ET. It has been shown first that there are subtle functional abnormalities indicating a cerebellar malfunction in ET. The triphasic pattern underlying ballistic movements shows distinct abnormalities resembling the situation in cerebellar disease. It was observed that both the onset of the antagonist activity, which is normally breaking the agonist movement, and the activity of the second agonist are delayed. The resulting movement abnormality is an overshoot, and this is a feature typical for cerebellar pathology. Another approach was to study the kinesiology of hand movements in ET. Voluntary target movements show an intention tremor that is indistinguishable from cerebellar tremor in almost half of the patients with ET. Despite earlier clinical description of these features this has never been interpreted as a sign of cerebellar malfunction. Additionally, there is a slowness of voluntary movements and hypermetria, which can be regarded as a further argument for a cerebellar dysfunction in ET. Subsequently the gait of patients with ET has been assessed, and as expected, the abnormalities of bipedal regular gait are only mild but are significantly abnormal. However, the tandem gait of patients with ET shows gross abnormalities (Fig. 1) with an increased number of missteps and other features typical for cerebellar gait. These abnormalities are preferentially found in ET patients who also have intention tremor, possibly indicating an abnormality of cerebellar gait control despite intention tremor of the leg is not seen in these patients. We have interpreted these findings to reflect a progressive cerebellar disturbance in ET, depending on the severity of the condition. If intention tremor develops in the setting of ET, we assume a disturbance of the cerebellar feed-forward control, which has been introduced earlier as a possible cause of tremor. Due to rhythmic discharges of the cerebellar output nuclei or even the whole olivocerebellar system, the cerebellar control of hand movements and gait may no longer be functioning regularly.

Meanwhile, it is generally accepted that ET is a central tremor. For individual patients, this can be demonstrated by spectral analysis of the accelerometer and electromyography (EMG). As in all central tremors, the EMG peak frequency will not shift when the extremity is loaded. Unfortunately this finding cannot always be demonstrated in early ET; thus, the distinction between ET and enhanced physiological tremor may be difficult in the early phase.

The Vim and Vop are the preferred and established targets for functional neurosurgery with both lesioning or DBS. The success of this approach is well-documented. However, the pathophysiological basis for this success is unclear. As the Vim is the target of the pallidothalamic outflow, essential tremor was suggested to be produced within the basal ganglia loop and parkinsonian tremor to be produced within the cerebellar loop but the supporting data for this hypothesis are poor. For years stereotactic lesioning has been focussed to include the Vim and the zona incerta, a region through which pallidothalamic and cerebellothalamic fiber tracts pass. Hassler and colleagues put the hypothesis forward that part of the effect is due to a lesion of the cerebellothalamic tract passing through the zona incerta. Recently two successfully treated patients have been described who had their DBS electrodes in the border zone of the zona incerta and the Vim. Similarly, the most effective electrodes with deep brain stimulation in Parkinson’s disease have been localized at the lower border of the zona incerta just neighboring the subthalamic nucleus (Volkmann et al., personal communication). Thus, from clinical experience, the zona incerta seems to be a crucial structure. Lesioning and stimulation of this structure seem to be equally effective with respect to tremor. As we do not know how stimulation works, either removal or high-frequency stimulation of the cerebellothalamic or the pallidothalamic bundle may be responsible for the therapeutic effect on tremor. The influence of these projections onto the tremor-producing network may take place at thalamic or at cortical levels. Other targets for thermocoagulation have been assessed in the early times of lesonal surgery but no conclusive results were reached. Therefore, further animal research assessing the interaction of cerebellar and basal ganglia output may be the key to answer the question why Vim/zona incerta surgery works. It may also help to answer whether other
FIG. 1. Direct tracings of markers attached in projection on the fifth metatarsal bone of both feet in a view from above (see schematic drawing in the upper center of the figure) for healthy subjects (HC), patients with ET and predominantly postural tremor (ETp), essential tremor with intention tremor (ETit), and cerebellar disease (CD). Recordings were made during tandem walking on the treadmill over 20 seconds of continuous measurement. Note the dysmetric and even ataxic leg movements in ETit and CD. (From Stolze et al., 2001)
locations such as cerebellar structures might be better targets for DBS in ET.

DYSTONIC TREMOR

Despite many studies on dystonic tremor, this type remains still a poorly classified entity. It has recently been defined clinically as a mainly postural/kinetic tremor in an extremity or body part that is affected by dystonia and that is usually not seen during complete rest. These are mostly focal tremors with irregular amplitudes and variable frequency (mostly below 7 Hz). Very rarely rest tremors may also occur.

A typical example of dystonic tremor is tremulous spasmodic torticollis (or dystonic head tremor). In many patients with dystonic tremor, “gestes antagonistes” or “trick maneuvers” lead to a reduction of the tremor amplitude. This approach can be used to separate dystonic “trick maneuvers” lead to a reduction of the tremor amplitude. This approach can be used to separate dystonic tremor from essential head tremor. The tricks are less common in dystonic tremors of the extremities, and it has been proposed that these tricks may be related to the basic mechanisms underlying dystonia rather than being a specific feature of dystonic tremor only. We are far from having a clear idea of how this tremor is generated, but it may be related to the mechanism of dystonia most likely generated within the basal ganglia loop.

Reports on the treatment of dystonic tremors are rare because the target symptom in these cases is usually dystonia. Mostly the patients have been operated within the pallidum internum (pallidotomy or DBS) but at least one recent case was also successfully stimulated within the Vim. One of our own cases, who presented with dystonic tremor but only mild dystonic signs, is now stimulated bilaterally in the Vim. This strategy led to a successful control of tremor but dystonic signs persist and show even some progression. One of the most important questions to be answered by clinicians is whether pallidal procedures can block dystonic tremor as effectively as tremor in PD. This mechanism would point at a significant disturbance of the basal ganglia loop for the generation of dystonic tremor. Even more than with other tremors, the location of the deep brain electrodes in dystonic tremor is based on clinical experience only.

CEREBELLAR TREMOR

Cerebellar (intention) tremor is diagnosed according to the following clinical signs: (1) pure or dominant intention tremor, uni- or bilateral; (2) tremor frequency mostly below 5 Hz; (3) postural tremor may be present but no rest tremor. The most careful clinical study of cerebellar tremor in multiple sclerosis has confirmed and further extended these criteria.

Cerebellar tremor is often used synonymously with intention tremor, although various clinical expressions of tremor have been described for cerebellar disorders. The mechanisms underlying cerebellar tremors have been studied extensively in animals. The cerebellum was either experimentally removed or its function has been temporarily blocked by cooling or chemical agents. It has been shown with selective muscimol injections into deep cerebellar nuclei that the critical structure seems to be the globose-emboliform nucleus. Tremor-related activity in monkeys was found in the motor and somatosensory cortex and the globose-emboliform nucleus but not the dentate nucleus. Therefore, trans-cerebellar and transcortical loops seem to be involved. Because intention tremor persists after deafferentation in monkeys, the somatosensory loops cannot be the only source of intention tremor. Thus not only a feedback, but also a feed-forward control must be the critical function of the cerebellum, and it is likely that a cerebrocerebellar loop is the possible cause. The analysis of voluntary movements in animal experiments and patients with cerebellar lesions suggests that the major cause is a disturbed timing and grading of the activity of antagonistic muscles. Indeed, several studies are suggesting that long-latency reflexes are enhanced in cerebellar disease. Although this mechanism seems to be the most important mechanism, some arguments do also advocate an additional central oscillator mechanism for cerebellar tremor.

Cerebellar tremors are classically treated with lesions or DBS within the Vim. This location has been found empirically, but the results are much less convincing than for PD or essential tremor. Hassler and colleagues have pointed out, that the lesion of the zona incerta below the thalamus is mandatory for a good result of thermocoagulating lesions in cerebellar tremor. In a recent series, Alusi and coworkers have advocated the Vop with or without additional lesions to the zona incerta to be the preferred target for functional neurosurgery of cerebellar tremor. The mode of action of surgery onto this type of tremor is unknown. It may be speculated that the oscillations are similarly blocked as in the case of essential tremor.

HOLMES TREMOR

The description by Holmes of this tremor syndrome was among the first descriptions; hence, the name Holmes tremor was proposed recently instead of rubral or midbrain tremor, which were considered to be anatomically misleading. The following criteria apply to this tremor. (1) Rest and intention tremor are present with sometimes irregular presentation. In many patients postural tremor is also present. The tremor is often not as
rhythmical as other tremors. (2) Tremor is of low frequency, mostly below 4.5 Hz. (3) If the time when the lesion occurred can be identified (e.g., in case of a cerebrovascular accident), a variable delay (mostly 4 weeks until 2 years) between the lesion and the first occurrence of the tremor is typical.

It is generally accepted, that Holmes tremor is a symptomatic tremor which is known to occur after different lesions centered to the brainstem/cerebellum and thalamus. Two systems, the dopaminergic nigrostriatal system and the cerebellothalamic system must be lesioned according to pathoanatomical107 and PET data.108 As these systems can also be lesioned along their fiber tracts, this tremor might also be caused by lesions in other locations (even at multiple cortical sites). There are a few patients reported who had preexisting cerebellar lesions that led to a stable cerebellar deficit, subsequently developing an additional nigrostriatal deficit109–111 and, therefore, presented later with a Holmes tremor. Another case had unilateral removal of the cerebellum because of a Lindau tumor and developed Parkinson’s disease more than 10 years later, confirmed by reduced striatal dopaminergic terminals. He presented with classical parkinsonian tremor on the side with the preserved cerebellum but had Holmes tremor on the side with the removed cerebellum.112 This finding is strong clinical evidence that indeed both functional deficits, cerebellar and nigrostriatal, must come together to produce this specific form of tremor.

The functional deficits of these two systems, thus, are reflected by the clinical symptoms and some insights into the interplay of the cerebellum and the basal ganglia are provided by this form of tremor. The resting tremor is known to cease when voluntary movements are performed; this is no longer true when the ipsilateral cerebellum is affected and the resting tremor seems to spill into voluntary movements, giving rise to an intention tremor of the same frequency as the resting tremor. Thus the cerebellar influence on motor performance may to some extent compensate the deficits induced by basal ganglia pathology at least during voluntary activity. Moreover, the resting tremor frequency seems to be influenced by the cerebellum as it is usually below 4 Hz in Holmes tremor compared with frequencies between 4 and 6 Hz in parkinsonian rest tremor. It may be hypothesized that the cerebellar system can compensate the basal ganglia circuits during voluntary movements as far as tremor production is concerned.

Patients with Holmes tremor are lesioned or stimulated within the Vim. There are only a small number of patients who have been treated, and it seems to at least improve the tremor.97,113,114

**NEUROPATHIC TREMOR**

Neuropathic tremor is assumed if a patient develops tremor in association with a peripheral neuropathy and no other neurological diseases associated with tremor. Some forms of peripheral neuropathies tend to develop tremors more often than others. Especially demyelinating neuropathies (e.g., dysgammaglobulinemia neuropathies) are frequent causes of such tremors.115–119 The tremors are mostly postural and kinetic tremors with a frequency between 3 and 6 Hz in arm and hand muscles. The frequency in hand muscles can be lower than in proximal arm muscles in patients with gammopathies,120 which can also be used as an electrophysiological tool for the diagnosis of the condition. This finding can also be taken as an argument that tremor frequency may depend on the length of the reflex pathway; therefore, the pathophysiological principle of the tremor may be an abnormal reflex mechanism.

There are some animal models that present a combination of tremor and peripheral neuropathy but often with additional pathologic conditions of the central nervous system, such as the gracile axonal dystrophy (GAD) mouse mutant,121 the grey tremor mutant mouse,122,123 or the twitcher mouse124 that exhibit tremor, sensory ataxia, and paresis of the hindlimbs. But as the pathologic condition is mostly not limited to the peripheral nervous system, it is unknown which role the neuropathy plays for the development of these conditions. Physiologic analysis for these animal tremors is completely lacking.

In patients with dysgammaglobulinemia neuropathy, wrist tremor could be modulated by mechanical perturbations or median nerve electrical shocks; thus, a peripheral contribution by reflexes seems to be present.120

Simple voluntary wrist movements were of normal duration and peak velocity, but the kinematic profile was asymmetric. Each movement was associated with a triphasic EMG pattern in agonist-antagonist-agonist muscles but the duration of the bursts were prolonged and the onset of the second agonist was delayed. This observation is very similar to the findings in essential tremor but it is still unclear whether it is due to tremor, to the peripheral neuropathy found in these subjects, or to a secondary malfunction of the cerebellum. Finally, the cerebellum showed abnormal activation in this condition.120 These results support the hypothesis that distorted and mistimed peripheral inputs are among the important reasons for this tremor. The finding of abnormal cerebellar activation may indicate that the central processing of the afferent information is defective or it is reflecting peripheral tremor.

Considering all the data together, it seems clear that
the central pathways are normal in these patients and the major pathological state seems to be the peripheral slowing and possibly distortion ofafferent signals. It may be hypothesized that, in contrast to cerebellar disease, not the feed-forward control of movement but the feedback control is the cause for the rhythmic disturbance in these patients. However, as only a minority of patients with severe peripheral neuropathies is developing tremor a further—and hitherto unknown—pathological condition must be present to produce this tremor.

Most of these patients have only a slight tremor; there are no formal studies available. Some need medical treatment; however, some of them are completely resistant to medical treatment. For these patients, surgical treatment may be discussed. We are not aware of any patient with this malignant tremor who has received functional neurosurgery.

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