REVUE NEUROLOGIQUE XXX (2015) XXX–XXX

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EM|consulte
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General review

News and controversies regarding essential tremor

Actualités et controverses concernant le tremblement essentiel

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INFO ARTICLE

Article history:
Received 29 October 2014
Received in revised form
1 February 2015
Accepted 2 February 2015
Available online xxx

Keywords:
Essential tremor
Pathophysiology
Cerebellum

ABSTRACT

Essential tremor is the most common movement disorder in adults. It is characterized by a postural and kinetic tremor affecting the arms, but it can also affect other body parts. It evolves gradually and can be responsible for a functional impairment in activities of daily living. Its pathophysiology remains poorly understood and effective therapeutic options are limited. There are significant semiological variations between patients, and the term ''essential tremor'' seems to encompass a wide range of heterogeneous clinical phenotypes. The diagnostic criteria presented in 1998 are now challenged. Furthermore, there is a current debate concerning the etiology of this affection, as to whether essential tremor is a complex degenerative disorder or a functional reversible disorder of neuronal oscillation. In this review, we summarize some aspects of clinical, etiologic and therapeutic news, to better address the questioning on unravelling the clinical presentation and examine the current pathophysiological controversy in this disorder.

Mots clés :
Tremblement essentiel
Physiopathologie
Cervelet

RÉSUMÉ

Le tremblement essentiel est le plus fréquent des mouvements anormaux de l'adulte. Il est caractérisé par un tremblement postural et d'action affectant les membres supérieurs, mais pouvant aussi atteindre d'autres parties du corps. Il évolue de façon lentement progressive et peut être responsable d'un handicap fonctionnel dans les activités de la vie quotidienne. Sa physiopathologie demeure mal connue, et les options thérapeutiques efficaces sont limitées. Il existe des variations sémiologiques importantes entre les patients, et le terme de tremblement essentiel englobe un ensemble hétérogène de phénotypes cliniques. Les critères diagnostiques décrits en 1998 sont aujourd'hui remis en cause. Par ailleurs, il existe actuellement un débat concernant l'étiologie de cette affection, qui oppose l'hypothèse

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http://dx.doi.org/10.1016/j.neurol.2015.02.007

Please cite this article in press as: Boutin E, et al. News and controversies regarding essential tremor. Revue neurologique (2015), http://dx.doi.org/10.1016/j.neurol.2015.02.007

neurodégénérative à celle d'une origine plutôt fonctionnelle. Cet article reprend quelques aspects des actualités cliniques, étiologiques et thérapeutiques, afin de mieux aborder le questionnement du démembrement clinique, et la controverse physiopathologique dans le tremblement essentiel.

Tremor is an involuntary rhythmic motor activity by which a body part exhibits a regular oscillatory movement. Tremor is defined by the movement's frequency, localization and mode of activation, at rest, during an ongoing action or when maintaining an attitude. Many causes of tremor have been described. Among them, essential tremor (ET) corresponds to the most common movement disorder observed in adults. Nevertheless, our current knowledge about the underlying pathophysiology remains sparse, and effective treatments are limited. This article resumes some of the new data that has become available concerning the clinical, etiological and therapeutic aspects of ET in order to better examine the current controversy about the degenerative or functional etiology of this pathological condition.

1. Definition of essential tremor: towards new clinical criteria?

ET is characterized by a postural and kinetic tremor of the upper limbs, sometimes involving the head (30%) and more rarely the face, voice, trunk and legs. Age, family history of tremor and Caucasian ethnic background are risk factors for ET [1–3]. Age of onset has a bimodal distribution, with a first peak in the 20–40 years age range and a second higher peak after 65 years [4]. Prevalence estimates have been quite variable, mainly because of difficult diagnosis and access to care. In the most reliable epidemiology studies, the estimated prevalence of ET is around 400 per 100,000 inhabitants, rising sharply with age to exceed 4600 per 100,000 inhabitants over the age of 65 years [5]. Despite its prevalence, less than one-third of affected people seek medical care [6]. Patients attending neurology clinics or tertiary centers probably have atypical or more severe forms of ET.

The diagnostic criteria set forward in 1998 in the Consensus Statement on Tremor describe ''a bilateral, largely symmetric postural or kinetic tremor involving hands and forearms, that is visible and persistent'', excluding other abnormal neurological signs, notably a dystonic component or task-specific tremor [7]. The course is slowly progressive, the intensity increasing with age, and in general potentially extending from the peripheral areas to the central axis. The tremor can have a functional impact impairing activities of daily living such as writing, drinking, or dressing. Characteristically, the tremor worsens with physiological or emotional stress, receding temporarily after ingestion of alcohol in half of patients. The diagnosis is essentially clinical. Polygraphic electromyography (EMG) using surface electrodes to record several muscles simultaneously can be coupled with a continuous accelerometric recording of the movement. Polygraphic recordings of ET display a 6–10 Hz postural tremor with an additional intentional component [8]. The rhythm is slower in the elderly subject and for more proximal muscles.

The diagnosis of ET requires a duration of at least 5 years, and formal exclusion of differential diagnoses: exacerbation of physiological tremor; iatrogenic, cerebellar or psychogenic tremor; dystonic tremor.

In clinical practice, presentations are quite variable depending on age of onset, extension beyond the upper limbs or to the voice, frequency of head tremor, responsiveness to alcohol, and association with cerebellar motor symptoms or non-motor symptoms. The current diagnostic criteria are not precise and lead to including a number of heterogeneous conditions under the term of ET. Two studies have reported high rates of misdiagnosis of ET, reaching 37% and 50%, respectively [9,10], most often in patients with Parkinsonism or dystonia. Dystonic tremor is defined as a postural or kinetic tremor appearing in a body part that is affected by dystonia, with irregular amplitude, variable frequency (generally < 7 Hz), and disappearance with complete rest [7]. When head or voice tremor predominates, it can be difficult to distinguish between different variants of ET, or between ET and dystonia (tremulous spasmodic torticollis, laryngeal dystonia). The presence of an antagonist movement is an argument in favor of dystonia [11]. Tremor associated with dystonia occurs in patients with a focal dystonia, but in a part of the body not affected by dystonia; for example a patient with spasmodic torticollis also presenting postural tremor of the upper limbs. Task-specific tremor, such as primary writing tremor (tremor appearing solely when writing), could be a form of dystonic tremor. It is highly important to have precise limits for the definition of ET: is dystonic tremor a form of ET or an entirely different entity? Can patients with isolated neck or voice tremor or with a very asymmetrical tremor of the upper limbs be considered to have ET or must we insist on finding some dystonic component? In this situation, using clinical criteria alone seems to be insufficient; other electrophysiological explorations are needed to analyze the tremor to determine whether it has an irregular amplitude or frequency, included myoclonic elements, or is associated with co-contraction of agonist/antagonist muscles suggestive of dystonia.

Several recent studies show that tremor may not be the only clinical manifestation of ET and that there is a more diffuse underlying neurological process.

1.1. *Cognitive deficits*

Gasparini et al. were the first to demonstrate, in 2001, significant abnormalities in cognitive function, e.g. frontal function, in patients with ET; they showed that in comparison with healthy controls, these patients exhibit lower performance levels on

Please cite this article in press as: Boutin E, et al. News and controversies regarding essential tremor. Revue neurologique (2015), http://dx.doi.org/10.1016/j.neurol.2015.02.007