REVIEW ARTICLE

Is essential tremor a single entity?

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Keywords:
classification, essential tremor, genetics, pathophysiology, review

Received 19 August 2017
Accepted 1 September 2017

European Journal of Neurology 2018, **25:** 71–82

doi:10.1111/ene.13454

Essential tremor (ET) is a frequent movement disorder. The new tremor classification has subdivided ET into the classical form with bilateral action tremor of the hands with or without involvement of further tremor locations and without any other explaining signs or symptoms for the tremor and into 'ET plus' which comes additionally with further neurological signs of unknown origin. This will provide a better foundation for subclassifying the condition. The immediate cause of ET is a preformed oscillating network within the central nervous system as revealed with electrophysiological methods. The reason why this network is getting into the tremor mode is unclear. Pathology has so far not convincingly proved neurodegeneration for the condition but possibly adaptive changes of the brain particularly in the cerebellum are likely. Genetics have not yet provided insight into the molecular causes of the condition but several genetic diseases presenting with an ET syndrome have been uncovered. Treatment options cover medication (propranolol, primidone, topiramate) and surgical interventions with deep brain stimulation, gamma-knife surgery and the recently introduced magnetic resonance imaging guided focused ultrasound lesioning. Further progress is awaited from the better integration of large prospective cohort assessment and basic science studies on the possible etiologies. In particular, aging-related tremor may explain a large number of the patients seen in clinical practice. Currently ET is considered a clinically relatively uniform condition with presumably various underlying etiologies.

Introduction

The term essential tremor (ET) has been used since the 19th century [1] and was finally established by Critchley in 1949 [2]. ET traditionally labels a condition with a slowly progressive action tremor but without significant other complaints and without a known etiology. The term 'essential' labels conditions that are clinically well described and despite appropriate diagnostic work-up have no known etiology (e.g. 'essential hypertonus'). It is within the logics of this naming that many hitherto unknown etiologies are underlying this condition and with more insight entities behind this label will shrink. Relatively newly discovered etiologies for patients with a clinical ET syndrome are patients with fragile-X-tremor-ataxia syndrom (FRATAX) [3] or mutations of the NOS3 or FUS gene. A recently described 'aging-related tremor' may turn out as a further subgroup [4]. Indeed, earlier definitions of ET by Critchley in 1949 [2] and Marsden [5] still included dystonic tremor or postural tremor of Parkinson's disease (PD). During the past decades the diagnostic criteria have been refined and ET was first contrasted against other tremor entities in the Movement Disorder Society 1998 tremor classification [6] which was recently updated in 2017 [7]. Marsden stated in 1983 that 'essential tremor is not a single entity' [5]. This paper summarizes the current answer regarding this question. Despite a quite homogeneous clinical picture, it is considered an umbrella term rather than a unique entity.

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EUROPEAN JOURNAL OF NEUROLOGY

Epidemiology

Essential tremor is a common disorder affecting ~1% of the general population and ~5% of the population over 65 years of age according to the current definitions [6]. The incidence curve has a first peak early in life and then steadily increases after the age of 50 [8,9]. A considerable portion of ET patients report a positive family history. The extent of heritability diverges widely with an estimated range between 20% and 90% [10–12]. It has repeatedly been shown that male gender predisposes to develop ET. Males tend to be affected more severely from hand tremor [13]. Both female gender and hand tremor severity increase the odds for head and/or voice tremor [14–16]. A German–Danish epidemiological study has shown that late-onset patients have a shorter life expectancy and earlier cognitive disturbances [4]. This subgroup was called aging-related tremor (replacing the old term 'senile tremor'). In a large clinical cohort, patients with a late tremor onset had a faster disease progression, less frequently reported alcohol sensitivity and a positive family history [17].

Clinical features and definition

An approximately symmetric postural or kinetic tremor involving the hands and forearms is mandatory for the diagnosis. The second most common additional tremor localization is the head (~25%) followed by voice tremor (~15%) and other localizations such as face, chin, legs (together below 10%) [16,18]. There are few ET patients with isolated head tremor [14,19].

Tremor severity varies greatly. ET may cause a significant psychosocial impairment with a strong impact of tremor on the patient's life but many patients do not even consult a physician due the mildness of their tremor.

The clinical course is slowly progressive. Until the end of the last century, the neurological literature did not mention other symptoms. Since then studies comparing non-tremor controls with ET cohorts found a number of subtle abnormalities, which can be grouped into cerebellar disturbances with a mild disturbance of tandem gait, subclinical oculomotor disturbances, a mild extremity dysmetria and disturbances of timing. A second group of abnormalities might indicate neurodegeneration or faster aging, e.g. shortened life expectancy or higher incidence of cognitive decline (mild cognitive difficulty through to frank dementia). A third group covers mild psychiatric disturbances (higher incidence of depression, apathy and personality characteristics). Finally, there is a group of findings needing further confirmation such as earlier hearing loss or olfactory disturbances. The pathogenetic implications will be discussed later but this has led to a more cautions definition of ET than earlier [2,5,6] bearing in mind the possible heterogeneity of ET which has been recently defined as [7] (i) isolated tremor syndrome of bilateral upper limb action tremor with or without tremor in other locations (e.g. head, voice, lower limbs), (ii) with a duration of more than 3 years and (iii) the absence of other neurological signs (e.g. dystonia, ataxia and parkinsonism) which can explain the tremor.

The exclusion criteria are isolated focal tremors (voice, head), orthostatic tremor with a frequency >12 Hz, task- and position-specific tremors, sudden tremor onset and stepwise deterioration.

There is an ongoing uncertainty about the meaning of clinically detectable additional findings in subgroups of ET, like mild dystonic or ataxic signs which do not suffice to make a syndrome diagnosis. Therefore the new classification proposes to keep them as a separate entity called 'Essential tremor plus' which is defined as tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, tremor at rest, questionable dystonic posturing, memory impairment or other mild neurological signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis.

Important differential diagnoses

Due to the absence of biomarkers, imaging or genetic parameters ET is diagnosed only on clinical grounds [6]. The lack of reliable diagnostic markers and the high prevalence of phenocopies entail the risk of misdiagnoses. The approach to tremor involves a patient history and a neurological examination focused on the nuances of tremor phenomenology. To characterize the patient's tremor it is particularly important to ascertain the main tremor component [18]. Postural, kinetic, intention or resting tremor may be a clue for the differential diagnosis. Tremors in which action tremor is predominant and those where resting tremor is the main tremor component should be differentiated. When rest tremor is present it should increase during movement onset rather than decrease as in PD [20]. Amongst the action tremors ET, dystonic tremor and enhanced physiological tremor due to metabolic disturbances or drugs are the most frequent tremors followed by functional tremor and tremor in neuropathy. PD is the most common form of resting tremor, along with drug-induced resting tremor. Table 1 gives an overview of the main differentials of ET and their characteristics. Besides the phenomenology

Table 1 Differential diagnosis of essential tremor

	Essential tremor	Monogenetic syndromes with postural tremor	Enhanced physiological tremor			Dystonic tremor	Neuropathic tremor	Functional tremor
			Toxin-related	Metabolic	Drug-induced			
Family history	Frequent	Possible, depending on inheritance pattern	No	No	No	Rare	Rare	Rare
Cause	Unclear, multiple causes possible	1. Well documented: fragile X syndrome; Roussy–Lévy syndrome; Wilson's disease; SCA 6, 12; DYT 5a, 6, 11, 24; VPS35; PARK2; NBIA2; PINK1; ATP13A2; PARK7; DNAJC6, FBXO7, aceruloplasminemia 2. Genes potentially associated with an ET phenotype in single tremor families: FUS; SORT1; SCN4A; NOS3; KCNS2, KV9.2; HAPLN4, BRAL2, USP46	Alcohol, arsenic, dichlorodiphenyltrichloroethane (DDT), lead, toluene, cocaine	Hypoglycaemia, B-12 deficiency, hyperthyroidism, hyperparathyroidism, hypocalcemia, hyponatremia, kidney disease, liver disease, alcoholism	Antiepileptics, antidepressants (e.g. tricyclics), beta agonists, neuroleptics, metoclopramide, lithium, antiarrhythmics, immunosuppresants, theophylline, thyroid hormones, withdrawal of drugs	Unclear, tremor occurring in ~20% of subjects affected from dystonia, monogenetic dystonias with tremor see monogenetic syndromes	IgM-neuropathy, CIDP, Guillain–Barré syndrome, plasmocytoma, amyloidosis	Unclear
Spontaneously reversible without drug treatment	No	No	Possible	Possible	Possible	No	Possible	Possible
Focal or segmental tremor	No	May occur	No	No	No	Yes	No	Mostly
Frequency, Hz	5–8	4–7	4–10	4–12	4–12	3–7	4–8	Variable frequency
Geste antagonistique	No	Depending on cause	No	No	No	Frequent	No	No
Alcohol sensitivity	70%	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No
Electrophysiological tools	Rare	No	Loading-invariant peak of the frequency spectrum in non-central tremors			Possibly	Neurography	Yes
Remarks		1. Often other pathognomonic combinations of symptoms 2. So far independent replication in other families lacking	Recording of detailed medical history and professional activity	Exclusion of metabolic condition at the time of initial neurological examination; liver disease may cause other tremor syndromes	Some drugs may also cause other tremor syndromes (rest tremor, cerebellar tremor)	Two forms: 1. dystonic tremor – dystonia and tremor in the same extremity; 2. tremor associated with dystonia – tremor in a body part that is not dystonic	Electrophysiological examination (neurography, mostly demyelinating neuropathies)	Sudden onset

CIDP, chronic inflammatory demyelinating polyneuropathy.

a detailed patient history and a description of the course, duration and dynamics of the disease help to classify it. Additionally, electrophysiological tremor analysis using (detecting load-invariant central tremor components, specific electromyographic patterns) laboratory analyses (to exclude metabolism-related tremors) and rarely brain imaging or genetic analyses to exclude other tremor causes may help to ensure the correct diagnosis [21].

Pathogenesis

Pathophysiologically abnormal oscillations of a tremor network including the cerebellum, brainstem, thalamus and sensory-motor cortex (Fig. 1) are well established based on clinical, electroencephalographic, magnetoencephalographic and functional imaging data [22–25]. Oscillations are then transmitted to the spinal motor neuronal pool [26]. This corticomuscular coherence has been proved for both proximal and distal muscles [26,27]. Two clinical arguments support this network view. First, small strokes anywhere within this network can alleviate contralateral tremor [28]. Secondly, deep brain stimulation (DBS) and focused ultrasound coagulation targeting the ventral intermediate (VIM) nucleus are established treatments for ET and reduce the tremor amplitude. Recordings from deep brain electrodes during procedures in the VIM nucleus of the thalamus neurons have shown rhythmic bursts of neuronal activity that are correlated with electromyographic tremor activity [29,30]. These studies have shown the cortico-bulbo-cerebello-thalamo-cortical circuit to be the main source of central tremorogenic oscillations [22,31]. Recently structural and functional magnetic resonance imaging (MRI) studies showed a correlation of grey matter decreases of the cerebellum and increases of cortical areas with clinical features of ET [32].

The reasons why this network is oscillating are less clear. The most likely explanation is abnormalities of gamma-aminobutyric acid (GABA) transmission as suggested by animal experiments, biochemistry in human tissue and imaging findings. GABA subunit alpha 1 (GABA(A)) is highly expressed in mammalian brain tissue and is the major inhibitory neurotransmitter in the central nervous system. GABA(A) receptor alpha 1 knockout mice exhibit postural and kinetic tremor and motor incoordination that share characteristics of ET in humans [33,34]. In postmortem tissue of ET patients the concentrations of both GABA(A) and GABA(B) receptors were reduced in the cerebellum but only the GABA(B) receptor concentration is inversely correlated with the duration of ET features in the dentate nucleus, suggesting that the loss of GABA(B) receptors follows the progression of the disease [35]. Positron emission tomography has revealed increased GABA(A) receptor binding of ^{11}C-flumazenil at the GABA(A) receptor sites reflecting reduced GABA-ergic function in the ventrolateral thalamus, the dentate nucleus of the cerebellum and the premotor cortex in ET [36,37]. Supplying GABA(A) agonist muscimol via microinjection into the ventralis intermedius thalamus reduces tremor amplitudes [38].

The major arguments against a GABA mechanism underlying the abnormal oscillations are the relative lack of efficacy of GABA-ergic medications for ET and the fact that extensive genetic studies could not

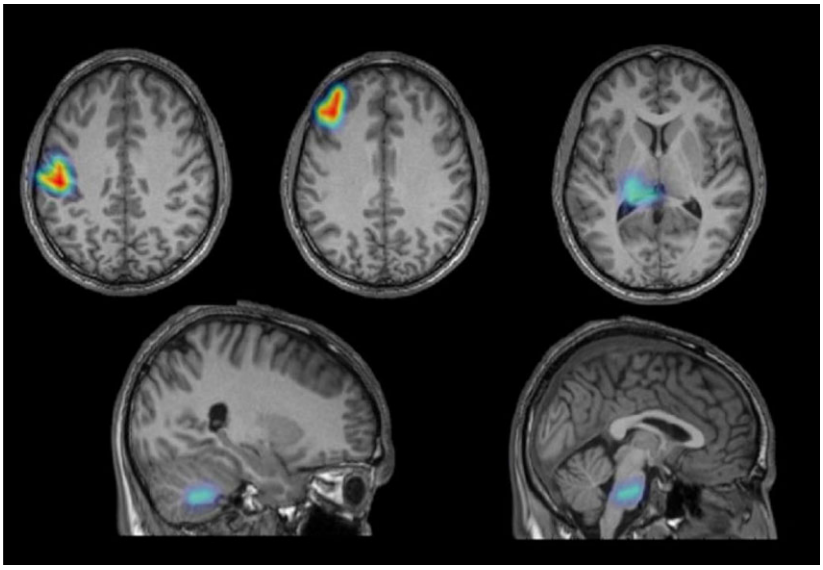

Figure 1 The coherent network of sources for a patient with essential tremor. Modified after [25].

detect an association between GABA(A) receptor and GABA transporter genes with ET [39,40].

In the past the inferior olive has frequently been suggested to cause oscillatory activity based on a GABA-ergic inhibitory mechanism. A well-documented property of olivary cells is to develop rhythmic activity [41] and harmalin-evoked tremor in rats is due to the loss of GABA-ergic activity within the inferior olive [42–44]. But the olive was never found to be involved in the oscillatory network of ET and, although many strokes in and around the inferior olive occur spontaneously, no ET patients have been reported so far who lost their tremor after such strokes [28]. Additionally one neuroanatomical study was unable to show any differences between the inferior olive of ET patients and controls [45]. Therefore, this possibility is becoming less likely.

Meanwhile a number of monogenetic diseases have been identified which can present with the clinical picture of ET at least for some time and need to be considered as a possible etiology in a newly diagnosed patient. In earlier days they were covered under the term ET. The most important of these conditions are listed in Table 1. Genetic testing is recommended only if further clinical signs for the appropriate etiology are discovered and/or if there is a suspicious family history.

Genetics

In large population-based studies ET occurred both sporadically and in families following an autosomal dominant trait [2,46,47]. The heritability of ET was analyzed with twin studies. For monozygotic twins a pairwise concordance rate between 0.60 and 0.93 and for dizygotic twins 0.27 and 0.29 suggests a high heritability [48,49]. The rate of families reporting a positive family history for ET, however, varies widely between 20% and 90% [10,12,50,51]. The reason for this may be difficulties in identifying symptom carriers unequivocally: clinical studies examining the heritability in ET showed that an anamnestic 'family history' of ET beyond the monozygotic condition is an uncertain parameter to make the final diagnosis 'ET' [52]. Considering the high prevalence of ET, phenocopies have to be assumed in both sporadic and familial ET [53]. Consequently, clinical assessment and identification of phenocopies is a precondition for successful genetic analyses in ET.

The method of choice to confirm heritability in large families consisting of several generations is a linkage study which can detect candidate regions and rare genetic variants with a large effect. The logarithmic odds ratio (LOD) score reflects the probability that disease phenotype and the genetic marker are co-segregating. In general, a LOD score >3.3 is required in the finding study and a LOD >2 in the replication study. Linkage analyses of ET families revealed linkage to three chromosomal regions: chromosome 13q13 (ETM1) which mapped in 16 Islandic families with a cumulative LOD score across all families of 3.71 [54], chromosome 2p24 (ETM2) which mapped in a very large Czech/American family with a LOD score of 5.92 [55] and chromosome 6p23 (ETM3) which mapped in a large American family with a LOD score of 2 [56]. Amongst these studies only ETM2 shows a convincing LOD score [57]. Thus, all candidate regions remained unconfirmed and no causative genetic variant was detected.

Whole-exome sequencing (WES) established in the early 2000s investigates the whole protein-coding regions of the genome. Analyzing the total DNA sequence allows rare genetic variants which are related to a disease to be identified. In contrast to linkage analysis WES may also be applied in smaller families with fewer generations. So far this method has been applied in several ET families [58–61]. The genes are listed in Table 1.

To test for the association of common DNA variants with sporadic ET genome-wide genotyping of single nucleotide polymorphisms (SNPs) is used (a genome-wide association study, GWAS). The first GWAS in ET performed in a small Icelandic population comprising less than 500 individuals found an association between ET and SNPs in the region of LINGO1 [62]. Replication studies did not consistently support this association, but SNP rs9652490 which in the initial study had reached genome-wide significance in both was also confirmed in one meta-analysis assessing all association studies and genotyping studies in ET [57]. LINGO1 has a role in neuroprotection and the protein is increased in the ET cerebellum [63–66]. A second GWAS found an associated SNP in SLC1A2 coding for the excitatory amino acid transporter 2 (EAAT2) which is necessary to terminate excessive activation of glutamate receptors and to maintain proper synaptic activation in the brain [67]. EAAT2 is increasingly expressed in the inferior olive and in the dentate nucleus [68]. The largest GWAS so far encompassing 3000 patients and 6000 controls of European and North American descent showed association with SNPs in three chromosomal regions near STK32B, PPARGC1A and CTNNA3 [69]. STK32B coding for a serine/threonine-specific protein kinase was increasingly expressed in the cerebellar cortex of patients. Recently the leading SNPs in STK32B (rs10937625) and in PPARGC1A (rs17590046) were replicated in an independent Asian cohort encompassing almost 1000 cases and 500 controls [70–72].

Despite considerable efforts there are no genes that are definitely related to ET [73]. To achieve conclusive results in genetic studies of ET multinational collaboration, common data elements for phenotyping ET and larger samples are needed to elucidate the full allelic spectrum and the estimated heritability.

Pathology

Accepted neurogenerative diseases such as PD or Alzheimer's disease are characterized by pathognomonic pathological findings in defined brain regions. The pathological study of ET is in its infancy and therefore many methodological problems are limiting the interpretations. Cross-sectional autopsy studies have examined relatively small case numbers following different protocols with varying end-points [74,75]. Only predefined brain regions such as the cerebellum, the brainstem including the inferior olive and the locus coeruleus have been examined so far [74,76]. Information about the age of onset, disease progression, accurate phenotype, additional neurological signs etc. are often missing. Different approaches to analyzing the brain samples including different case–control definitions, different staining protocols and different methods for microscopic analysis were applied. These are some of the reasons for conflicting observations.

The historic case descriptions of the last century showed no coherent pathology (for a review see [77]). Meanwhile three centers have started to study the pathology of ET in a systematic way (Saskatchewan/Canada; New York/USA; Sun City/USA). The attention of all three groups is focusing on the cerebellum and in particular on possible Purkinje cell reduction. A statistically significant Purkinje cell reduction was repeatedly reported by one group [74] with neuropathologically advanced methodology [78]. But this core finding could not be reproduced by the other two teams [79,80] and at least one of them had a large sample of 56 cases and were also using the latest neuropathological methodology [80]. Loss of neurons is the hallmark of degeneration and a loss of neurons is a necessary but not sufficient condition for the pathological diagnosis of neurodegeneration. If such a loss of neurons is not even reproducible between different investigators, there is no reason to consider ET a neurodegenerative disease.

A second group of findings has been dealing with the anatomical microstructure of the input to and output from Purkinje cells. So far, this has been studied only by the New York group but in admirable detail. The first findings were abnormal Purkinje cell torpedoes (ovoid swellings of the proximal portion of the Purkinje cell axon) and morphologically abnormal axonal signs. The torpedoes were correlated with tremor duration in ET cases with age of onset <40 years [81] but this finding awaits further interpretation. Abnormalities were also found for the climbing fiber and parallel fiber connections with Purkinje cells. Climbing fibers usually terminate mainly on the proximal dendrites of Purkinje cells but are known to be highly modifiable under certain conditions of the adult mammalian brain [82]. In ET they are more concentrated on the distal dendrites and this finding is inversely correlated with tremor severity. Interestingly, this inverse correlation is lost in ET patients treated with DBS confirming the plasticity of these relations [83]. The comparison of ET with PD, spinocerebellar ataxia type 1 and multiple system atrophy patients showed that PD and ET had an increased number of distal climbing fiber terminations whilst multiple system atrophy and spinocerebellar ataxia type 1 patients had fewer climbing fibers terminating in the distal territory [84]. These complex findings await final interpretation but currently this is interpreted as evidence for plasticity of the cerebellar connections in ET. It is unlikely to be a sign of neurodegeneration if reversible under DBS.

So far the anatomical areas outside the cerebellum have not been a matter of detailed studies. The only exception is the brainstem, in particular the locus coeruleus which is also a nucleus which may have an importance for tremor [85]. Here parvalbumin, a biochemical marker of GABA-ergic activity, was reduced compared to controls whereas there was no difference in cerebellar parvalbumin [86]. Loss of inhibition within this nucleus may be a factor for tremor production.

In one of the autopsy studies Lewy bodies in the brainstem, mainly in the locus coeruleus, were found in a subgroup of ET patients [74]. However, these patients with Lewy bodies were significantly older at the time of brain examination than those cases without Lewy bodies and therefore incidental Lewy bodies may be the explanation for this finding. Another study could not find an increased incidence of Lewy bodies in ET cases [75].

To further define the neuropathological characteristics of ET larger numbers of prospectively collected phenotypic and pathology data representing a wide range of clinical states (such as pure ET cases with an early disease onset, ET cases with a late disease onset and transitional forms between ET and PD) are needed to ensure clinico-pathological correlations.

Treatment and management of ET

As the cause of ET is still unexplained there are no causal therapies. The decision to treat the tremor

should be based on the patient's impairment due to the tremor which does vary widely between different individuals and does not correlate with the tremor amplitude. Often, tremor patients are satisfied with a comprehensive explanation about their disease and the information that ET is not PD.

Medical treatment

Medical treatment leads to a reduction of tremor symptoms in 50% of patients but rarely to complete disappearance of tremor symptoms [87]. This needs to be communicated with patients to avoid disappointment. Medical treatment often has a better effect in patients with low amplitude tremor than for individuals with high amplitude tremor. Intention tremor has a major impact on patients' disability. Empirically intention tremor responds worse to oral medical treatment than pure postural tremor. ET may impact on numerous aspects of daily function and modern studies should include both a clinical severity score and a patient-reported outcome, usually a disease-specific quality of life score, the QUEST [88].

First-line treatment in ET are non-selective β-blockers such as propranolol and primidone [87,89]. Both medications have been evaluated by multiple controlled randomized and placebo controlled studies [90–92]. In young tremor patients propranolol is the medication of choice. Propranolol (20–240 mg daily dosage) is contraindicated in patients suffering from heart disease or asthma bronchiale and may lead to erectile dysfunction in male patients [93]. In older patients primidone 62.5–500 mg (daily dosage) is usually applied (Figs 2 and 3). An acute toxic reaction to primidone with drowsiness, ataxia and dizziness can be reduced or avoided by slowly increasing medication (starting dose 62.5 mg in the evening and slow increase). Propranolol and primidone can be given in combination (each increased to the highest tolerated dose). Medications of second choice include topiramate (50–300 mg) and non-selective β-blockers such as metoprolol [94–96].

The treatment of axial tremor symptoms is challenging. Head tremor usually responds poorly to propanolol and primidone. In some cases botulinum toxin A treatment of neck muscles is successful. In patients with orally refractory head tremor botulinum toxin A has been efficient [97]. Essential voice tremor may also be treated with a combination of oral tremor medication and injection of botulinum toxin A into

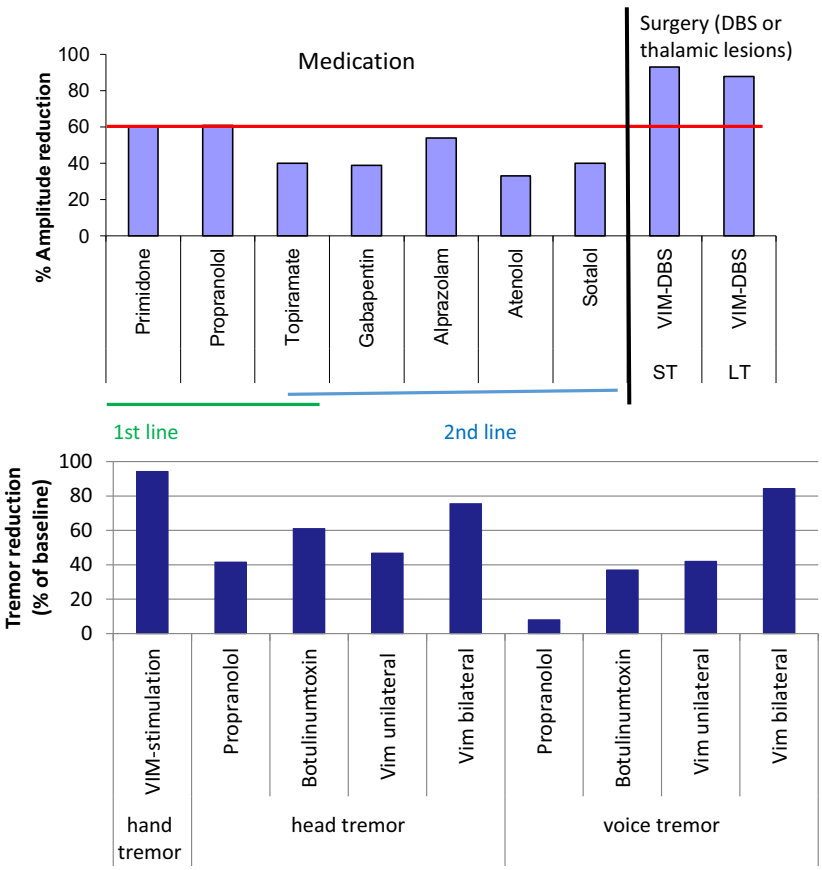

Figure 2 Efficacy of interventions for essential tremor. The effect strengths are taken from a recent review [87].

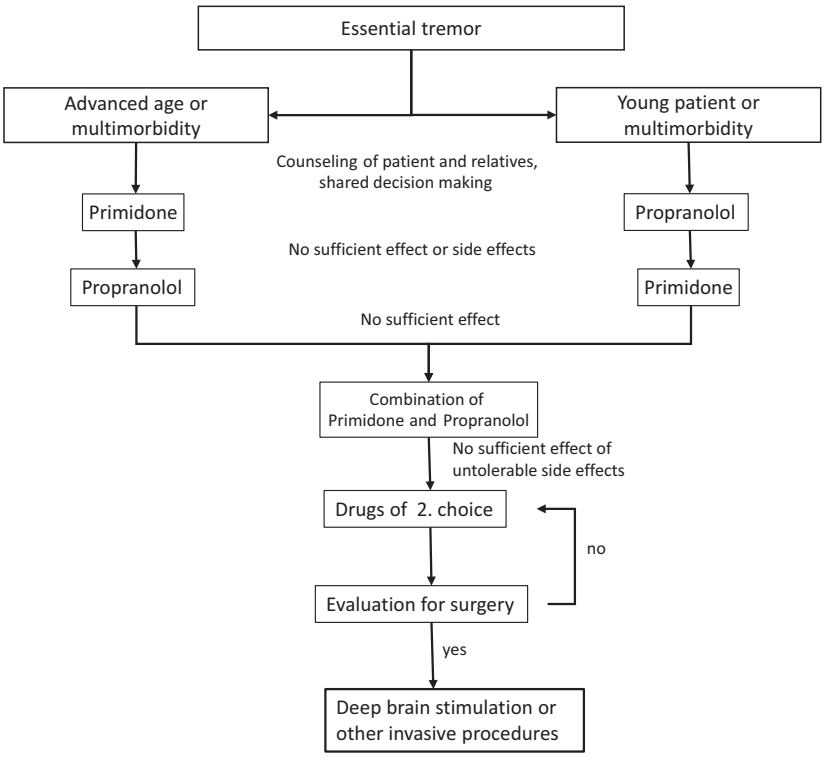

Figure 3 Treatment algorithm for essential tremor.

the vocal cord but comes with the risk for swallowing difficulties [98,99].

Functional neurosurgery

It has long been known that lesioning of the VIM nucleus of the thalamus or in the adjacent subthalamic region of the zona incerta can improve most tremors and in particular ET [100]. It is beyond the scope of this paper to discuss the pathophysiological background in detail. In this region, the most likely tract system mediating tremor alleviation is the dentato-thalamic tract and not only lesioning but also continuous stimulation of an electrode placed in this region can improve tremor. This is the bottleneck of the nervous system where many hyperkinesias are improved. All types of interventions are all targeting this same region. Lesional surgery with thermocoagulation through temporarily placed probes is nowadays only rarely performed. DBS is currently the best evaluated treatment with least side effects. Gamma-knife radiation [101] and the recently developed MRI-guided focused ultrasound thermocoagulation are only available in a few centers. Thermocoagulation is not covered here but the other three treatments.

In 50% of ET patients, oral medication does not help significantly. For those, DBS can be considered for severely handicapped subjects affected with hand and arm tremor, with intention tremor or for head/voice tremor. Electrodes are implanted stereotactically in the VIM nucleus of the thalamus or in the adjacent subthalamical region of the zona incerta and continuously stimulated with rectangular pulses between 130 and 180 Hz. The effect of DBS in ET has been examined in several uncontrolled trials showing an excellent long-standing effect on tremor amplitude [102,103]. If hand tremor is the most important symptom unilateral stimulation may be justified but whenever axial symptoms like head and voice tremor are the target symptom bilateral electrodes are needed [87]. Side effects include all kinds of surgical complications (e.g. bleedings >2%, infections of the system <5%) and stimulation induced side effects (voice and gait changes, ataxia). The latter can be corrected with adaptation of stimulation [104]. In some patients there is a waning of the stimulation effect and there is an ongoing discussion whether this is due to tachyphylaxia or to disease progression [105]. New hardware holds the promise that stimulation can be better customized to each patient [106].

In a few centers VIM lesioning with gamma-radiation is offered [101]. It is an incision-free but invasive therapy. Late complications with slowly extending lesions have been reported and more extensive experience is needed. Focused ultrasound thalamotomy with magnetic resonance imaging guidance (MRgUST) is the latest incision-free but again invasive treatment of ET and has been examined in several case series and in

one randomized controlled trial [107]. Focused ultrasound reduces hand tremor in patients with ET without affecting fine motor function. Follow-up studies show a sustained excellent response for an observation period >6 months. Side effects include sensory and gait disturbances [107,108]. Long-term results are still pending. DBS and MRgUST seem to be equally effective for the target symptom hand tremor, but MRgUST can only be applied unilaterally because of the risk of side effects after bilateral thalamic MRgUST lesions whilst DBS stimulation parameters can be adapted. As head and voice tremor cannot be sufficiently treated with unilateral procedures, thalamic MRgUST may also not be sufficiently efficient. DBS has a known risk for bleeding and other side effects whilst for MRgUST bleeding has so far not been described. It is a promising therapy but it is invasive and more studies will help to finally compare the treatments.

Future prospects

Research for ET is in an exciting stage. Recent progress and needs for future research were summarized during a National Institutes of Health conference in 2015 [8]. The paucity and heterogeneity of recent research findings in almost all fields reported in this review are most probably due to the heterogeneity of the disease. One of the important needs is therefore to better characterize possible subgroups of ET. This may be with clinical, epidemiological, genetic or other basic science dependent markers. Promising candidates for a clinical subgrouping are patients with head and voice tremors [109]. Epidemiology and clinical cohort assessment has shown that probably the largest subgroup of patients is the one with aging-related tremor [4]. If this hypothesis holds true one important cause of tremor may be a form of aging presenting with tremor as a main symptom (a scientifically justified version of the old 'senile tremor'). Movement disorder research and aging research may meet here. Studying the pathology of ET shows promising findings. Besides the search for convincing signs for neurodegeneration, this research may explain the adaptive changes of the brain to the ongoing tremor [84]. Genetic research will depend on the organization of large worldwide cohorts. This will be the first task of the newly created Tremor Study Group of the International Parkinson and Movement Disorder Society.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest. Outside this topic GD has received lecture fees from Almirall and Novartis and has been serving as a consultant for Boston Scientific. He received royalties from Thieme publishers. He receives funding through his institution from the DFG and Medtronic.

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