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Current status and future development direction of treatment for essential tremor

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Abstract. Essential tremor (ET) is a common movement disorder that continues to increase in prevalence. Currently used drugs such as propranolol and primidone have limited efficacy and are associated with a high number of side effects. For individuals with serious conditions, deep brain stimulation (DBS) is an effective therapy, but its high cost and potential surgical complications limit widespread use. Emerging therapies including Magnetic resonance-guided focused ultrasound (MRgFUS) and Gamma Knife radiosurgery thalamotomy (GKT) offer new options for treatment, but their long-term effects still need to be proven. Future treatment directions should focus on personalized and low side-effect regimens to enhance patients' quality of life. This article reviews existing treatments and discusses future directions.

Keywords: Essential tremor, Pathogenesis, DBS, Treatment development.

1. Introduction

An uncontrollably occurring oscillatory behavior is called tremor and unfixed amplitude appearing in a certain body part. Essential tremor often appears in the form of action tremor or postural tremor and shows progressive development. The disease gradually progresses from involving symmetrical upper limbs to involving the head and voice. Although it has no serious impact on the life cycle of patients, it often affects their daily lives and work, bringing great inconvenience to them. At present, the cause of essential tremor is not entirely understood, but it is known that it is an autosomal dominant familial genetic disease, and is simultaneously affected by genetics and acquired environment. [1] The prevalence of essential tremor in France and the United Kingdom was examined by certain researchers and found that the standardized incidence rates in the United Kingdom and France are similar, which are 19.51 (18.97 - 20.01) and 19.50 (18.97 - 20.05) respectively. Moreover, the elderly have a greater incidence rate than the young, and men have a higher incidence rate than women. It is also found that the incidence rates in both countries are on an upward trend. [2] Essential tremor is usually considered as a clinical syndrome. At present, the main diagnostic elements include the patient must have isolated tremors of the arms and hands for three years or more. Additional tremors in areas including the head and lower limbs may or may not appear during the disease process, and there is no other neurological dysfunction. Neurological conditions like Parkinson's disease are excluded. For example, the patient must have isolated tremors of the arms and hands for three years or more. [3] At present, the main treatment methods for essential tremor include drug treatment and surgical treatment. The first-line drugs for drug treatment are propranolol and primidone, which are mainly suitable for patients with mild to moderate symptoms. The surgical treatment method is DBS (Deep Brain Stimulation), which is

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mainly suitable for severe patients. Drug treatment is the conventional treatment method for essential tremor, but the curative effect of drug treatment is often not ideal, and there may be many side effects, such as dizziness, nausea, fatigue, etc., which limit the application range of drug treatment. [3] Between 2015 and 2019, approximately two million patients with essential tremor were diagnosed in the United States. Among them, only about one million patients received treatment. Among the patients who received drug treatment with propranolol and primidone, about 40% of the patients interrupted taking the medicine for various reasons. The main reasons are drug side effects and poor efficacy. [4] This article's goal is to go over the benefits and drawbacks of the most recent essential tremor therapies, with a view to providing new insights into the management of this condition.

2. Pathogenesis

Essential tremor is caused by a combination of complicated neuropathologic processes, environmental variables, and hereditary factors. The DRD3-Gly-9 gene variant on chromosome 3q13.3 was discovered to be closely linked to the development of essential tremor. The gene is heritable, with purebred inheritors leading to earlier onset or greater severity of the disease, and its expression level is positively correlated with age. The DRD3-Gly-9 gene variant, which has an almost 100% ectopia in older age groups, may cause dopamine overexpression and thus more strongly inhibit the regulation of gamma-aminobutyric acid (GABA) activity on Purkinje cells in the cerebellar cortex. DRD3 receptors are present in both the cerebellum and basal ganglia, but DRD3 abnormalities in the cerebellum are thought to be more likely to be associated with the development of essential tremor [5].

Environmental factors likewise also have a significant part in the development of essential tremor. Harmane, a dietary β-alkaloid abundant in meat, is commonly used to create a model of essential tremor in animals. Research has indicated a substantial correlation between the emergence of essential tremor and blood Harmane concentrations. [6] In addition, according to a Spanish research, smokers had just half as much essential tremor as nonsmokers, and the highest smokers had a prevalence one-third that of nonsmokers [7].

The pathophysiologic mechanisms of essential tremor have not been fully defined. While cerebello–thalamo–cortical network was once thought to be the key pathological loop in essential tremor, more recent studies have pointed out that this mechanism involves a much broader neural network including the cerebellum, thalamus, motor cortex, precuneus, inferior parietal lobule, and insula, and that together, these brain regions form a cerebellar pivot, the function of which is implicated in most of the pathophysiological features of essential tremor [8]. There are three main hypotheses used to describe the mechanism of tremor production in essential tremor: The neurodegenerative hypothesis, the Central oscillatory network hypothesis, and the GABA hypothesis. The neurodegenerative hypothesis suggests that the development of essential tremor is closely related to age and that patients may be at a higher concomitant risk of Parkinson's disease and dementia. The central oscillatory network hypothesis proposes that certain neurons in the central nervous system have unique electrophysiological properties, where hyperpolarization of their membranes can lead to oscillations at specific frequencies and form oscillators that drive tremors. The GABA hypothesis, on the other hand, emphasizes that GABA transmission or receptor dysfunction triggers abnormal activity in cerebello–thalamo–cortical network, which causes tremor [9].

3. Medication Treatment

3.1. Propranolol

Propranolol can block beta receptors and is considered one of the primary medications used to treat essential tremor [10]. Propranolol is more effective in hand tremor, but less effective or even ineffective in head tremor. Commonly used doses of short-acting or long-acting propranolol 60mg to 200mg per day can result in 50%-70% relief of tremor symptoms in 50% of patients [3, 10]. Propranolol works well and remains effective for several years in some patients, but is progressively less effective or even ineffective in others, particularly in individuals who are older than 60 [11]. The target of action of

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propranolol may be located at central or peripheral β-receptors, but its exact mechanism of action is not clear [12]. Studies have shown that the antitremor effect of propranolol is not related to plasma concentration but to the dose taken, and that increasing the dose improves efficacy. Adverse effects of propranolol include hypotension, bradycardia, syncope, fatigue, depression, and erectile dysfunction, and contraindications include asthma, chronic obstructive pulmonary disease, and congestive heart failure [13].

3.2. Primidone

Primidone is an anticonvulsant and among the first-line medications used to treat essential tremor [10], It is more effective in hand tremor but generally effective in head tremor [3]. Primidone acts by acting on the GABAergic system, but the exact mechanism is not fully understood [14]. Primidone can be metabolized to phenobarbital in vivo, but its antitremor effects are not thought to be related to phenobarbital [15]. Primidone can be used as an alternative drug in patients who are not sensitive to propranolol, but its onset of action is prolonged and its effect is related to the concentration of primidone in the blood, and excessive conversion to phenobarbital may attenuate the antitremor effect [16]. Acute adverse effects of primidone include sedation, fatigue, nausea, and ataxia, which are dose-independent and may be induced even when used in small doses [15].

3.3. Other drugs

In patients for whom propranolol and primidone are ineffective or inefficient, 'second-line' agents such as topiramate and botulinum toxin type A may be considered [13]. The anticonvulsant topiramate may have an antitremor mechanism that involves blocking voltage-dependent calcium and sodium channels and improving GABAergic transmission. [17]. Topiramate significantly improves upper limb tremor, enhances motor task performance, and improves dysfunction, but there are adverse effects such as sensory abnormalities, taste reversal, inattention, decreased appetite, and memory difficulties [18]. Botulinum toxin type A treats dyskinesia by inhibiting the release of acetylcholine and significantly reduces hand, head tremors after injection, but may also trigger adverse effects such as head and neck pain, muscle weakness, and dysphagia [19].

4. Surgical Treatment

Deep brain stimulation (DBS) is indicated for serious patients who have failed medication and is widely used for its effectiveness in controlling arm and head tremors [3]. DBS is a neurosurgical procedure that allows neuromodulation based on targeted circuits and is the standard treatment for Parkinson's disease, essential tremor and dystonia. The DBS system, which consists of intracranial electrodes, extension wires and pulse generators, has evolved over the last two decades [20]. Common anatomical targets for DBS include the ventral intermediate nucleus of the thalamus (VIM), the caudal zone of indeterminacy (cZI), and the posterior subthalamic area (PSA).While the advantages of DBS lie in its modifiable, reversible, highly effective, and relatively safe features, its disadvantages should not be overlooked, such as the invasive nature of the procedure, the need for general anesthesia, the stringent patient selection criteria, and the risk of surgical complications, including speech disorders, dysphagia , ataxia and gait disorders. Some patients may develop tolerance after chronic VIM stimulation and need to increase the intensity of stimulation to maintain efficacy, whereas PSA stimulation does not seem to cause tolerance and the effect can be maintained for several years. [21-22]

5. Emerging Therapies

5.1. Magnetic resonance-guided focused ultrasound (MRgFUS)

Transcranial magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging non-invasive therapeutic technique for patients with drug-refractory essential tremor, in which a focused ultrasound beam generated by a multicomponent transducer induces thermal ablation of the target tissues. MRgFUS is able to cauterize the tissues without penetrating the skin and skull, thus offering the advantage of

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avoiding hemorrhage and infection, and it is also comparatively inexpensive [21]. This method has shown significant efficacy in improving hand and nystagmus, and has been used in the Chinese population, with postoperative follow-up demonstrating its effectiveness in relieving tremor [23]. However, studies have also found that tremor is prone to recurrence and cannot be adjusted after recurrence, requiring multiple surgical treatments, although most patients remain willing to undergo reoperation [24]. In addition, there are some limitations to the use of MRgFUS, for example, patients with a low mean skull density ratio (SDR) and patients who are unable to undergo MRI scanning are not candidates for this treatment [21].

5.2. Gamma knife radiosurgery thalamotomy (GKT)

Gamma Knife radiosurgery thalamotomy (GKT) is a radiosurgery technique used for the treatment of essential tremor. GKT is carried out while under local anesthetic, using a 4 mm collimator to apply high doses of radiation of 130-152 Gy to the ventral intermediate nucleus of the thalamus (Vim), and is appropriate for patients with comorbidities of severe medical conditions such as anticoagulant use, or for patients who have failed to respond to other therapeutic means [25]. Studies have shown that the effect of symptomatic relief after GKT is slightly weaker than that of MRgFUS, and the tremor of some patients has not been significantly improved, and there is variability in the therapeutic effect [26]. Nevertheless, GKT has fewer postoperative complications, such as motor weakness and dysarthria, than MRgFUS, mainly because the GKT surgical target is more precise and less likely to damage the surrounding tissues, whereas the target of MRgFUS is more irregularly shaped, which may lead to a series of complications caused by damage to the internal capsule [26].

6. Discussion

Treatment of essential tremor varies depending on the severity of the patient's condition and tolerance of treatment. Pharmacological treatment is indicated for mild to moderate patients and exhibits a quick start to activity, but long-term use is limited by the occurrence of side effects, such as cardiovascular adverse effects of propranolol and central nervous system adverse effects of pramipexole. Deep brain stimulation (DBS) is a more effective option for patients who are ineffective or intolerant of pharmacological treatments, especially for severe patients, but its invasive procedure, high cost and postoperative complications limit its use. Emerging treatments such as MRgFUS and GKT are potential alternatives to pharmacological and DBS treatments with their non-invasive advantages, especially for patients who are not suitable for pharmacological or unwilling to undergo DBS surgery, but the stability of their efficacy and long-term results still need to be further evaluated.

Comparison of traditional and emerging surgical techniques shows that DBS is more effective, but the indications for surgery are narrower and the surgical risk is higher; Emerging therapies such as MRgFUS and GKT are somewhat less effective, but their non-invasive nature makes them potential options for patients. Future research should focus on the development of drugs with fewer side effects and longer-lasting efficacy to improve patient compliance, as well as exploring the clinical application of non-invasive therapies, especially the further optimization of MRgFUS and GKT, in order to increase their therapeutic reliability and to reduce postoperative complications. In addition, personalized treatment plans for different genetic factors and types of tremors will be an important direction to improve the outcome of essential tremor treatment in the future.

7. Conclusion

Essential tremor is a prevalent movement ailment, causing all kinds of inconveniences in work and life for patients around the globe. Despite recent advances in research, the exact cause, pathogenesis, and optimal treatment of this disorder are still not fully understood. Currently, drugs are the predominant treatment for essential tremor, with first-line medications including propranolol and primidone, but the side effects of both, as well as insensitivity in some patients, limit efficacy. Surgically, deep brain stimulation (DBS) is the most widely used surgical tool, but its invasive nature, strict patient screening criteria and postoperative complications have led to increased interest in novel technological tools.

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Emerging treatments such as Magnetic resonance-guided focused ultrasound (MRgFUS) and Gamma Knife radiosurgery thalamotomy (GKT), although they have been used in the clinic, their therapeutic efficacy still needs to be further optimized and validated, especially with regard to the duration of maintenance of efficacy and the occurrence of complications in the postoperative period. Future research should focus on the development of novel drugs with fewer side effects and significant efficacy, and explore the use of personalized therapies, especially for patients with significant genetic backgrounds, research into gene-targeted drugs or surgery may accelerate a complete cure for the disease. The combination of personalized treatment with novel non-invasive therapies may hold new promise for remedies for essential tremor to improve the quality of life for patients and enhance their long-term prognosis.

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