Rehabilitation in Essential Tremor

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Introduction

Essential tremor (ET) is one of the most prevalent disorders in neurology, affecting 0.4–0.9 % in the general population of all ages, reaching even higher prevalence with advancing age, ranging from 4.6 to 6.3 % for individuals above 65 years old [1]. Although the term "benign ET" was historically used to describe it as a monosymptomatic disorder with no pathological changes on brain tissue examination, it is not unusual to observe cases in which the progressive and potentially disabling nature of ET is evident, leading to significant disability and affecting quality of life with prominent interference with activities of daily living. In addition, there is heated debate about the validity and caveats of a series of recent studies highlighting the possible pathological changes in addition to a high prevalence of nonmotor symptoms and imaging abnormalities. Another recent development in the understanding of this field is the general concept that the entity as a single disease may not exist and what we refer to as ET is in fact the phenomenological expression of a series of different disorders [2, 3].

In spite of controversies and significant developments, treatment remains limited and includes pharmacotherapy, surgery and nonpharmacological therapy. The focus of this review is to discuss non-pharmacological therapies, mostly related to rehabilitation.

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H.F. Chien, O.G.P. Barsottini (eds.), *Movement Disorders Rehabilitation*,
DOI 10.1007/978-3-319-46062-8_6

Clinical Features of ET

The phenomenological hallmark of ET, as its designation suggests, is the postural and kinetic tremor of the upper extremities present in up to 95 % of cases. However, any body part can be affected, including more commonly the head (30 %), lower extremities (10–15 %), and voice (20 %), in the vast majority of cases in combination [4]. The two most consistent risk factors for ET are age and a family history of tremor. In spite of ≥50 % of the affected individuals presenting a positive family history, the objective identification of genes related to increased susceptibility and monozygotic forms of ET has been difficult [5]. Recent studies have linked LINGO1, FUS, and TENM4 genes with a higher risk of developing ET; however, further studies are needed to confirm their pathogenicity [6].

As mentioned above, in recent years, studies have shown that individuals with ET may develop nonmotor symptoms, such as cognitive deficits, depression, anxiety, balance disorder, hearing impairment, olfactory dysfunction, and sleep problems with a significant impact on quality of life [7]. Again, these topics and studies are currently a matter of heated debate among experts in the field.

The same observation is valid for pathological changes in ET. These findings in the central nervous system include a reduction in cerebellar Purkinje cells and restricted Lewy bodies in the locus ceruleus in a limited number of autopsied cases [8]. Brain imaging also shows changes in the cerebellum. A recent study using functional MRI and EEG showed an association between tremor and activity in the ipsilateral cerebellum and contralateral thalamus [9]. However, pathological and imaging changes are still a matter of controversy in the literature.

Pharmacological and Surgical Therapies

Pharmacological Approach

Oral pharmacotherapy in ET comprises different medications, including beta-blockers, anticonvulsants (primidone and topiramate), and benzodiazepines. Treatment may bring varying degrees of improvement in tremor severity in approximately 50 % of the patients, although this proportion diminishes as the disease progresses to more severe stages [10]. In general, treatment choice is based on the degree of psychological, social, and functional disability, and according to the general health status, as all pharmacological choices carry a significant risk of inducing adverse effects.

First-line therapy agents include propranolol and primidone. Propranolol is a nonselective β-adrenergic receptor antagonist and is the only pharmacotherapy approved through the US Food and Drug Administration (FDA). Initial doses of 20 mg twice a day are usually recommended (10 mg, twice a day in elderly patients). Doses can be titrated up to 60–320 mg/day. Common side effects are bradycardia and bronchospasm. Primidone is an anticonvulsant drug and the initial dose is 50 mg at bedtime (25 mg in elderly patients). Typical maintenance daily dose is

250–750 mg/day. The most frequent side effects are somnolence and dizziness. Second-line therapies include benzodiazepines (i.e., alprazolam), gabapentin, pregabalin, and topiramate.

Botulinum toxin type A (BTXA) has been proven to be effective in ET patients with tremors of the upper extremities [4]. Furthermore, BTXA is also effective in ET patients with head and voice tremors.

Essential tremor is classically marked by alcohol responsiveness. Ethanol improves tremor at relatively low levels, usually within 20 min for 3–5 h, sometimes followed by a rebound tremor augmentation [11]. Alcohol provides reduction in tremor amplitude, but not frequency. Given the significant improvement in tremors, alcohol addiction needs to be monitored in ET patients.

Surgical Approach

Deep brain stimulation (DBS) is the surgical treatment recommended for patients with disabling ETs. In 1997, the FDA approved DBS as a treatment for ET [12]. The ventrolateral thalamus and the posterior subthalamic area (PSA) are the typical targets for DBS in ET. Compared with unilateral implants, bilateral implants significantly reduce tremors; however, with a higher risk of side effects from stimulation (balance and posture). The effect is safe, with effects that are quite significant and long-lasting in most cases [13]. Thalamotomy is a surgical option that is equally as effective for refractory tremors in ET patients, but is limited because of an increased relative risk of adverse effects, especially with bilateral surgery.

Nonpharmacological Therapy and Rehabilitation

Although symptoms of ET may be controlled with medication or surgical interventions, it is of interest to explore and employ additional forms of therapy to assist with functionality. As already summarized, both medications and surgical interventions have several potential side effects and may not provide the best benefits in terms of overall motor function. Therefore, rehabilitation is in the pipeline not only for ET, but for most chronic neurological conditions. The interventions described below should typically be used in parallel with other forms of treatment or as the sole intervention.

Tremor

Resistance Training

The resistance training (RT) program is an exercise intervention consisting of sessions of biceps curl, wrist flexion, and wrist extension movements performed with both limbs with sets of repetitions. Exercises may be performed with loads.

A preliminary study reported that fine manual dexterity and upper limb strength were improved in ET patients after an RT program [14]. The findings of this preliminary study provided initial evidence that RT is worthy of further investigation as a therapy for improving functionality in ET patients.

A recent study investigated whether a generalized upper limb RT program improves manual dexterity and reduces force tremor in older individuals with ET [15]. Ten ET patients and 9 controls were recruited to participate in a 6-week program of upper-limb RT. A battery of manual dexterity and isometric force tremor assessments were performed before and after the RT to determine the benefits of the program. The 6-week, high-load, RT program produced strength increases in each limb for the ET and healthy older group. These changes in strength were associated with improvements in manual dexterity and tremor, particularly in the ET group. The least affected limb and the most affected limb exhibited similar improvements in functional assessments of manual dexterity, whereas reductions in force tremor amplitude following the RT program were restricted to the most affected limb of the ET group. These findings suggest that a generalized upper limb RT program has the potential to improve aspects of manual dexterity and reduce force tremor in older ET patients.

Inertial Loading

Inertial loading has been postulated to have an effect on the strength of motor unit training and the synergistic/competitive interaction between central and mechanical reflex tremor components in individuals with ET. A research study recruited 23 patients with ET and 22 controls and first defined the one-repetition maximum (1-RM) load, which is the maximal load that can be successfully lifted (wrist extensors) through the full range of motion [16]. Subsequently, the participants were asked to hold their hand in an outstretched position while supporting sub-maximal loads (no-load, 5, 15, and 25 % of 1-RM). Hand postural tremor and wrist extensor neuromuscular activity (electromyography [EMG]) were recorded. Results showed that inertial loading resulted in a reduction in postural tremor in all ET patients. The largest reduction in tremor amplitude occurred at between 5 and 15 % loads, which were associated with spectral separation of the mechanical reflex and central tremor components in a large number of ET subjects. Despite an increase in overall neuromuscular activity with inertial loading, EMG tremor spectral power did not increase with loading. The authors concluded that the effect of inertial loading on postural tremor amplitude appears to be mediated in large part by its effect on the interaction between the mechanical reflex and central tremor components.

Dexterity Training

Another technique that has been evaluated is exercise involving fine dexterity. A recent study evaluated the effect of a short-term dexterity training (DT) program on muscle tremor and the performance of hand precision tasks in patients with ET [17]. The study consisted of three testing sessions: baseline, after 4 weeks without any interventions (control), and after 4 weeks of a DT program carried out 3 times per week. Eight patients with ET were recruited and the training program consisted of

12 dexterity training sessions, each session comprising four tasks, involving both goal-directed manual movements and hand postural exercises. ET-specific quality of life questionnaires and postural and kinetic tremor assessments were performed. Results showed improvements in the performance of the two goal-directed tasks ($P<0.01$); however, postural and kinetic tremors did not change. The authors concluded that DT could be effective in increasing fine manual control during goal-directed movements, but no changes in tremor severity were seen. The authors also claimed that one limitation might be the short training program (4 weeks) and training programs taking place over a longer period of time may be of greater benefit.

Transcutaneous Electric Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is currently used for analgesia in a broad range of medical conditions, such as peripheral nerve lesions, angina, dysmenorrhea, labor and delivery, osteoarticular diseases, burns, and some types of postoperative pain [18]. Despite its widespread clinical use, the physiological mechanism of action is not known, stimulating parameters are subjective, electrode placement is empirical, and most of all, its effectiveness is a subject of controversy. Regardless of these uncertainties, the use of TENS has been reported to be effective in anecdotal reports of cases with certain movement disorders, including ET. Unfortunately, the only study performed using standard objective methodology in 5 patients with ET and 2 with peripheral tremor, did not reveal any significant improvement in the tremor scale scores after TENS, nor did it show any statistically significant difference in the amplitudes of the accelerometer tracings [19].

Massage

A recent study examined the influence of massage therapy on the severity of ET using an activity-based rating scale pre- and post-treatment [20]. The study consisted of five consecutive weekly sessions. The subject, a 63-year-old woman, indicated her hands and head to be the primary areas affected by ET. The treatment aim was to reduce sympathetic nervous system firing; therefore, the massage techniques implemented were based on relaxation. Methods included Swedish massage, hydrotherapy, myofascial release, diaphragmatic breathing, remedial exercise education and affirmative symptom management recommendations. Drawings of an Archimedes spiral for comparison pre- and post-treatment provided an objective, visual representation of tremor intensity affecting fine motor control. Goniometric measurements were taken to mark changes in cervical range of motion. Results revealed that tremor intensity decreased after each session, demonstrated by improved fine motor skills. The client also reported increased functionality in the cervical range of motion, which was documented during the first and last visits. The authors suggested that tremors in ET might be related to symptomatic activity and can be reduced by initiatives that encourage a parasympathetic response. Therefore, massage therapy would be a valuable method of treatment for ET. However, the study only examined 1 patient and tremor severity can present in an irregular pattern owing to subjective individual triggers. Further controlled research studies are required to lessen the variability between subjects and to validate these findings.

Gait

Essential tremor is marked by kinetic, postural, and intention tremors; however, many studies have suggested an underlying dysfunction of the cerebellum or cerebellar system causing gait and balance problems. Older age (>70 years) was consistently found to increase the risk of balance and gait disturbances in ET [21].

Louis et al. [22] studied the functional aspects of gait in patients with ET, placing their findings within the context of two other neurological disorders, Parkinson's disease and dystonia, and comparing them with age-matched controls. The authors administered the six-item Activities of Balance Confidence (ABC-6) Scale, which is a self-administered questionnaire that scores the level of confidence in performing different activities, such as standing on tiptoes to reach for an object, or walking outside on icy sidewalks, without losing balance or becoming unsteady. They also collected data on the number of falls and near-falls, and the use of walking aids in 422 participants (126 with ET, 77 with PD, 46 with dystonia, and 173 controls). Results showed that balance confidence was lowest in PD, intermediate in ET, and relatively preserved in dystonia compared with controls. The number of near-falls and falls followed a similar ordering. Use of canes, walkers, and wheelchairs was elevated in ET and even greater in PD. The authors concluded that lower balance confidence, increased number of falls, and a greater need for walking aids are variably features of patients with range of movement disorder compared with age-matched controls. Although most marked among PD patients, these issues affected ET patients and, to a small degree, some patients with dystonia.

A recent study compared timing control of gait in ET patients versus controls, and further assessed the association of these timing impairments with tremor severity among the ET patients [23]. One hundred and fifty-five ET patients and 60 age-matched controls underwent a comprehensive neurological assessment and gait analysis, which included walking at a criterion step frequency (cadence) with a metronome (timing production) and walking at a criterion step frequency after the metronome was turned off (timing reproduction). Outcomes of interest for both conditions were timing accuracy (measured by cadence error) and timing precision (measured by cadence variability). Results showed that cadence was lower in ET patients than in controls ($P<0.03$), whereas step time was similar for ET patients and controls. Accuracy (cadence error) and precision (cadence variability) were not different in ET patients compared with controls. Cranial tremor score was significantly associated with cadence (timing production condition, $P=0.003$, and timing reproduction condition, $P=0.0001$) and cadence error (timing production condition, $P=0.01$). Kinetic tremor and intention tremor scores were not associated with gait measures. The study concluded that ET patients do not demonstrate impairments in the timing of gait control compared with matched controls, in keeping with the hypothesis that the cerebellum might be important for timing the control of discrete rather than continuous movements.

It is well recognized that ET patients have gait and balance impairment [24]; however, most of the studies published on nonpharmacological approaches involve patients with PD, only revealing a gap in the literature in terms of treatment of ET

gait disorders. Unmet needs in this field include randomized studies comparing ET patients and matched controls to assess the impact of physiotherapy and rehabilitation on gait and balance disorders in patients with ET.

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