Expert Overviews Provide Updates in Parkinson's Disease and Movement Disorders

Written by Muriel Cunningham

I. Classic essential tremor (ET) is a heterogeneous tremor syndrome without signs of other neurological impairment. The prevalence and the incidence of ET increase with age, with ≥5% of people aged >65 years estimated to have ET. Roger Elble, MD, PhD, Southern Illinois University School of Medicine, Springfield, Illinois USA presented a summary of ET and treatment options.

ET can be difficult to diagnose so information from a careful neurologic examination and drug history must be obtained to distinguish ET from other disorders such as dystonia and early Parkinson's disease [Schiebler S et al. *Mov Disord* 2011; Deuschl G et al. *Mov Disord* 1998]. Electrophysiologic testing can help differentiate ET from physiologic tremor, orthostatic tremor, cortical tremor, and psychogenic tremor. Dopamine transporter single-photon emission computed tomography is useful in distinguishing ET and dystonic tremor from early Parkinson's disease. Dr. Elble emphasized that anxiety and depression in patients with ET are common and should not be overlooked, because they often have a greater negative effect on quality of life than the tremor itself.

Pharmacotherapy for ET is limited and often inadequate. Primidone and propranolol remain the 2 most efficacious drugs for ET, with ~50% of patients responding to either drug. The responses can be dramatic but are typically not sustained, with efficacy diminishing over time. Some success has been obtained with topiramate treatment, but its use may be accompanied by cognitive impairment. Other agents such as zonisamide, levetiracetam, gabapentin, pregabalin, amantadine, benzodiazepines, methazolamide, flunarizine, nimodipine, clonidine, low-dose theophylline, clozapine, mirtazapine, 3,4-diaminopyridine, lacosamide, memantine, and carisbamate have been tested, but the results have been either inconclusive or negative.

Ventrolateral thalamic and subthalamic deep brain stimulation (DBS) is an effective option for patients with disabling tremor who have not responded to drug therapy. However, risks associated with DBS therapy include hardware infections (<6%), migration or misplacement of leads (<5%), lead fractures (<5%), skin erosion (~1%), symptomatic hemorrhage (~2%), lack or loss of efficacy, and side effects of stimulation. Additionally, the benefit of DBS, as with pharmacotherapy, often diminishes over time, particularly in women. In 1 study of 45 patients, 33 (73.3%) reported a declining benefit after a mean of 18.8±15 months (range, 3 to 75 months) [Shih LC et al. *Parkinsonism Relat Disord* 2013].

II. Claire Henchcliffe, MD, DPhil, Weill Cornell Medical College, New York, New York, USA, gave an overview of Parkinson's disease (PD). An estimated 4.1 to 4.6 million patients are affected globally, with the number expected to more than double by 2030. The peak onset of PD is between the ages of 55 and 65 years. The hallmarks of PD include bradykinesia, rest tremor (in the majority), rigidity, and postural instability (later in the disease). These symptoms are usually asymmetric and respond to PD medications. Nonmotor symptoms such as constipation, hyposmia, mood changes, and rapid eye movement behavior disorder coincide with motor symptoms and are often apparent earlier in the progression of PD.

PD signs and symptoms may overlap with other neurodegenerative diseases, often leading to misdiagnosis. Biomarkers in development such as neuroimaging ligands and sophisticated biochemical and molecular techniques may lead to earlier and more accurate diagnoses of PD in the future.

A variety of drugs are used in the treatment of PD (Table 1). Nonpharmacologic approaches include surgery, lifestyle management strategies, and complementary therapies. DBS of the subthalamic nucleus is the most frequently performed surgical procedure for PD in the United States. Optimal candidates for DBS are those who do not have significant cognitive decline or psychiatric comorbidities. Persistent benefit in bradykinesia, rigidity, tremor, and dyskinesias can be obtained, but the declines in gait and balance continue. Evidence suggests that exercise has possible neuroprotective effects and should be encouraged. Patients with PD often use complementary therapies such as diet, dietary and herbal supplements, vitamins, massage therapy, acupuncture, and traditional Chinese medicine.

III. The third movement disorder discussed was dystonia. Dystonia is characterized by sustained muscle contractions affecting one or more body parts, resulting in abnormal postures. Dystonia may occur intermittently or persistently, and the severity may vary over time. Nutan Sharma, MD, PhD, Massachusetts General Hospital, Boston,

Table 1. Medications for Motor Symptoms of Parkinson's Disease

Medication	Mechanism of Action	Comments
Anticholinergic agents trihexyphenidyl, other	Anticholinergic activity	Improves tremor Care regarding side effects
Dopamine agonists pramipexole (IR, ER) ropinirole (IR, ER) rotigotine apomorphine	Direct binding to dopamine receptors	Monotherapy and adjunctive therapy Counsel patient about driving, ICD side effects Apomorphine is injectable Rotigotine is transdermal delivery
Levodopa carbidopa/levodopa carbidopa/levodopa ODT carbidopa/levodopa ER carbidopa/levodopa/entacapone	Dopamine precursor	Risk of motor complications Use of extended release not recommended for reducing off time (decreased bioavailability)
COMT-Inhibitors entacapone tolcapone	Inhibit peripheral levodopa breakdown	Adjunct therapy only Tolcapone requires monitoring for hepatic toxicity
Selective MAO-B inhibitors rasagiline selegiline Zydis selegline	Inhibit dopamine breakdown	Monotherapy and adjunctive therapy Long-term benefits suggested
Amantadine	NMDA receptor antagonist, other	Monotherapy and adjunctive therapy; decreases dyskinesias
Carbidopa	Inhibits peripheral levodopa breakdown	Administer with carbidopa/levodopa to reduce nausea side effect

COMT=catechol-O-methyl transferase; ER=extended release; ICD=impulse control disorders; IR=immediate release; MAO-B=monoamine oxidase B; NMDA=N-methyl-D-aspartate; ODT=orally dissolving tablet.

Table 2. Mutations Associated with Dystonia

Genetic Mutation	Inheritance	Phenotype
DYT1	AD	Childhood limb onset
DYT3	X-linked	Young adult focal onset Progression to multifocal/generalized Parkinsonism
DYT4	AD	Craniocervical dystonia with spasmodic dysphonia Thin face and body habitus Partially responds to EtOH and/or propranolol
DYT5	AD	Childhood limb onset Marked response to L-dopa
	AR	Childhood limb onset Developmental delay Motor response to L-dopa
DYT6	AD	Teen focal onset Progression to multifocal/generalized Speech abnormalities
DYT11	AD	Myoclonus and dystonia EtOH reduces symptoms
DYT12	AD	Rapid onset, Rostrocaudal gradient Bulbar symptoms
DYT23	AD	Childhood/teen onset Cervical dystonia, dystonic tremor of arms Laryngeal dystonia possible
GNAL (Gα-olfactory protein)	AD	Cervical dystonia with spread (to multifocal or generalized)

AD=autosomal dominant; AR=autosomal recessive; EtOH=ethanol.

Massachusetts, USA, presented the latest genetic classification and treatment information for patients with dystonia. The number of genes associated with dystonia continues to grow rapidly, and current genetic information is summarized in Table 2.

Several approaches may be used to treat patients with dystonia. Physical therapy for dystonia can be helpful and may include orthopedic bracing devices. Pharmacotherapy includes the anticholinergic triheyphenidyl or the benzodiazepines clonazepam, diazepam, or lorazepam. The dopaminergic agents carbidopa/levodopa should be administered to children with dystonia, but they have not been helpful in adult-onset dystonia. Tetrabenazine in daily doses of 50 to 100 mg may be helpful in tardive dystonia. In Dr. Sharma's experience, baclofen has been effective in treating cranial dystonias, but the sedating side effects outweigh any benefit in larger muscle dystonias.

Four different chemodenervation agents are currently available in the United States: onabotulinumtoxinA, incobotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB. Dr. Sharma stressed that the units of these agents are not interchangeable. "You really need to know which brand you're using, and what brand the person has been treated with before," said Dr. Sharma. Many patients respond to these medications provided the appropriate dose is administered and the correct muscles are targeted. Excessive weakness is a frequent side effect, but the risk of developing antibodies is minimized if injections are given at intervals of >10 to 12 weeks.

DBS is the surgical treatment of choice for dystonia patients who do not respond to medications or botulinumtoxin injections. The globus pallidus interna is the only approved site for DBS in dystonia. It takes at least 6 months to see maximal improvement, which is longer than the response time seen in patients with PD. In Dr. Sharma's experience, children with DYT1 have a dramatic response to DBS and continue to respond.