NEW HORIZONS

New horizons in the pathogenesis, assessment and management of movement disorders

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Abstract

In this review, we shall outline recent advances in our understanding of the movement disorders which geriatricians encounter in their clinical practice. Many of these diseases are no longer simply considered disorders of movement: carefully conducted longitudinal studies have shown that concomitant cognitive dysfunction, neuropsychiatric disturbance and behavioural issues are frequent and exert a heavy burden on the individual and their carers. Great progress has been made in understanding the molecular and cellular processes that drive the pathological changes in these conditions, as have advances in neuroimaging and preclinical drug discovery programmes. Unfortunately, this is yet to translate into disease-modifying therapies for these progressive disorders. Advances have been made in non-pharmacological interventions such as tailored physiotherapy and speech therapy programmes. The important contribution of palliative care has been recognised and increasingly incorporated into the multidisciplinary approach. The UK is at the forefront of research into these conditions and geriatricians are well placed to contribute to research through recruiting patients to observational studies or therapeutic trials, particularly with the support of agencies such as the National Institute for Health Research—Dementias & Neurodegenerative Diseases Research Network (NIHR-DeNDRoN).

Keywords: movement disorders, Parkinson’s disease, progressive supranuclear palsy, dementia with Lewy bodies, multiple system atrophy

Introduction

In this ‘New Horizons’ article, we will focus on the movement disorders which geriatricians encounter in routine clinical practice. We will outline recent advances in the clinic and laboratory and how these are translating into better understanding of the pathological processes driving these conditions, improved diagnostic accuracy and, ultimately, paving the way for the development of disease-modifying therapies.

Degenerative movement disorders

No longer considered purely disorders of movement, many patients will have co-existent cognitive impairments and neuropsychiatric disturbances which are equally troublesome for them and their carers. These degenerative proteinopathies, which are outlined in Table 1, are characterised by abnormal protein handling and oxidative stress with subsequent cell toxicity and death. Parkinson’s disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are synucleinopathies, whereas progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and some forms of frontotemporal lobe degeneration are driven by tau pathology. The clinical features are the manifestation of degeneration in select neuronal populations influenced by the distribution of pathology, the proteinopathy driving the disease and any co-existent pathological processes.

Synucleinopathies

Parkinson’s disease

PD is the second most common neurodegenerative disorder after Alzheimer’s disease [1]. The pathological hallmark
The incidence of PD increases with age [1], and an older age at onset is strongly associated with faster disease progression [4]. Accounting for only a small proportion of all cases, monogenetic forms predominate in those with young-onset PD and at least eight loci of importance have been identified with Genome Wide Association Studies [5]. Within the general population, a positive family history may be associated with certain clinical features; the H1 haplotype of the microtubule-associated protein tau gene confers an increased risk of dementia [7]. The UK-wide ‘Tracking Parkinson’s’ Study aims to recruit 2500 patients with new and young-onset PD to further define the importance of genetic factors in the development and progression of PD. Environmental factors such as solvents containing trichloroethylene [8] and pesticides [9] have been linked to PD and require further evaluation.

**Clinical advances**

The clinical features of PD encompass motor abnormalities, cognitive impairments, autonomic dysfunction and neuropsychiatric disturbances. Recent research has focused on motor phenotype classification and its correlation with pathology and patterns of disease progression. Four distinct clinical phenotypes have been described and are outlined in Table 1. Each is associated with a different disease trajectory: those with younger onset or tremor-dominant presentations appear to have a longer time interval to developing falls and dementia [10]. Patients with postural instability and gait difficulty typically develop falls and dementia sooner [11], however, these patients are often older and have more extensive cortical LB deposition [10].

Non-motor symptoms (NMS) are important predictors of the quality of life [12] and approximately half of NMS are not reported or recorded [13]. Using the 30-point NMS screening questionnaire (NMSQuest) in 545 patients across all stages of PD, Martinez-Martin et al. [14] reported nocturia to be the most prevalent NMS. Cognitive, perceptual, autonomic, sleep and sexual symptoms occurred in over 30% of patients. A recent incidence study highlights that those with very early PD experienced a greater number of NMS when compared with age-matched controls, and those with the postural instability gait disorder subtype of the disease had a higher burden than those with tremor-dominant disease (Khoo et al., submitted). The importance of recognising and managing NMS is emphasised in the National Institute for Health and Clinical Excellence Guideline on PD [15]. Many NMS predate the onset of motor dysfunction by many years [16], offering further insight into the development of PD and suggesting a ‘pre-motor phase.’ LBs have been found in the colon mucosa of those with PD up to 5 years prior to the onset of motor parkinsonism [17], possibly suggesting an intestinal route of entry with centripetal, or rostral spread. Constipation and disturbances of sleep, mood and olfaction are common and collectively may represent a Parkinson at Risk Syndrome, which is currently the subject of intense study, the ultimate goal being to identify those at highest risk of developing PD and allowing the rational targeting of future disease-modifying strategies.

**Cognitive and neuropsychiatric issues**

Dementia may ultimately develop in almost 80% of those with PD [18]. The pattern of cognitive deficits in Parkinson’s disease dementia (PDD) is very different from AD, with visual hallucinations, cognitive fluctuations and visuospatial dysfunction being core features. For research

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**Table 1. Classification of degenerative movement disorders according to protein aggregation**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Phenotypic variants and clinical presentations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synucleinopathy</td>
<td>Parkinson's disease: Early or young-onset; Tremor-dominant; Non-tremor dominant/Postural-instability and gait difficulty; Rapid disease progression without dementia</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Dementia precedes parkinsonism or occurs within one year of parkinsonism onset</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>MSA-Cerebellar variant; MSA-Parkinsonian variant; Pure Autonomic Failure</td>
</tr>
<tr>
<td>Tauopathy</td>
<td>Progressive supranuclear palsy: PSP-Richardson syndrome; PSP-Parkinsonism; Pure akinesia with gait freezing</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Corticobasal syndrome; PSP-like syndrome; Progressive non-fluent aphasia; Behavioural variant frontotemporal degeneration</td>
</tr>
<tr>
<td>Pick's disease</td>
<td>Behavioural variant frontotemporal degeneration; Semantic dementia; Progressive non-fluent aphasia</td>
</tr>
</tbody>
</table>
and clinical purposes, DLB is differentiated from PDD by the ‘1-year rule’ [19]: the diagnosis of DLB requires cognitive dysfunction to precede motor symptoms, or occur within 1 year of motor onset. In contrast to the motor manifestations of PD, which reflect dopaminergic deficiency, dementia is underpinned by a profound cholinergic deficiency, even greater than that seen in AD [20]. A recent Cochrane Review supports the use of cholinesterase inhibitors, with rivastigmine having modest benefits in global function, cognition, behavioural symptoms and activities of daily living in those with PDD [21]. For those with early PDD, the Health Technology Assessment programme funded UK-based multi-centre MUSTADD-PD trial will evaluate the effects of the early institution of donepezil and recruitment will begin shortly.

Subtle cognitive dysfunction or mild cognitive impairment (MCI) occurs in around a quarter of patients and is reported across all stages of PD [22]. PD-MCI is defined as a cognitive decline which, although, not normal for age, is still associated with essentially normal functional activities [22] and guidance for formal neuropsychological testing is available [23]. Single domain impairments occur more frequently than multiple domain impairments; attention and executive impairments are most commonly observed, in contrast to the general ageing population where amnestic deficits predominate [22]. Two longitudinal studies reported increased dementia risk in those with PD-MCI [7, 24]; however, further information from large observational studies is needed to inform the prognostic significance of PD-MCI.

Across all stages of PD, major depression is reported in 5–20% of patients, with a further 1–30% suffering minor depressive episodes [25]. The evidence base for treatment is limited, with trials often small and of short duration. Selective serotonin reuptake inhibitors are commonly prescribed and a recent placebo-controlled double-blind randomised controlled trial (RCT) of venlafaxine and paroxetine supported the use of both over placebo [26]. There is some evidence supporting tricyclic anti-depressants such as nortriptyline and desipramine in PD depression [27, 28], but their anti-cholinergic properties often make them unsuitable for this population. The anti-depressant properties of pramipexole have recently been recognised [29].

Impulse control disorders (ICDs) in those receiving dopamine agonists (DAs) are an increasingly recognised phenomenon. In a cross-sectional study of over 3,000 patients with PD [30], 13.6% of patients were identified as having an ICD, with 3.9% having two or more ICDs. Compulsive shopping was most prevalent (5.7%), followed by gambling (5.0%), binge-eating (4.3%) and compulsive sexual behaviours (3.5%). ICDs were more frequent in those prescribed a DA compared with other anti-parkinsonian medications, although it should be noted that this study consisted of subjects aged under 75, and therefore the applicability to older patients may be limited. Predominately associated with DA use, ICDs have been reported in patients receiving levodopa [51] and following deep brain stimulation (DBS) [32]. Risk factors for the development of an ICD include male sex, younger age and a history of gambling or depression, and these should be sought prior to the initiation of DAs and behaviours suggestive of an ICD should be enquired about regularly.

New treatments for PD

In general, the drug development pipeline for PD is relatively sparse, and almost 50 years after their introduction, l-dopa preparations remain the most effective form of oral therapy. Stem cell and gene transfer strategies have thus far proved disappointing. There is a need for better treatments to address not only the dopaminergic deficits, but also the other neurotransmitter derangements that occur within the cholinergic, serotonergic and noradrenergic systems. Table 2 shows some of the drugs currently being trialled for PD in Europe and North America. Disease-modifying drugs that slow the rate of dopaminergic nigral degeneration would simplify the management of motor problems; likewise slowing the onset of dementia and non-motor features would significantly enhance the quality of life for the individual and their carer.

DBS of the subthalamic nucleus (STN) is an established surgical option [33]. Key to its success is careful lead placement and patient selection: Patients should be under 70 with l-dopa responsive disease and no significant neuropsychiatric or cognitive disturbance, which unfortunately excludes a significant proportion of the population seen by geriatricians. STN stimulation has little impact upon gait dysfunction, axial symptoms and falls. Undergoing profound degeneration in PD, the pedunculopontine nucleus (PPN) provides significant cholinergic input to the basal ganglia and cortex [34] and may play an important role in posture and gait. A recent double-blind RCT [35] of unilateral PPN stimulation demonstrated benefit in terms of reducing falls, but not the overall UPDRS score; for this to be achieved, bilateral stimulation of the PPN and subthalamic region may be required [36].

Non-drug treatments

Trials of multidisciplinary rehabilitation and exercise are underway in the UK and Holland. Input from PD specialist nurses improves patients’ sense of well-being at no additional cost [37]. Speech and language therapy in the assessment and management of dysphagia is well-established, for quiet speech and dysphonia the Lee Silverman Voice Treatment may be beneficial [38]. Evidence is growing for the role of physiotherapy, which may be beneficial in improving gait, freezing and falls, but it is important to note that different strategies are required for different disease stages and experienced physiotherapists are essential [39].

Dementia with Lewy bodies

Dementia with Lewy bodies is characterised by fluctuating impairment of cognition, visual hallucinations and parkinsonism
<table>
<thead>
<tr>
<th>Drug Action</th>
<th>Trial name</th>
<th>Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-modifying Creatine Supports mitochondrial function</td>
<td>NET-PD NCT00449865</td>
<td>III</td>
<td>Measures of disease progression over 5 years Due to report in May 2015</td>
</tr>
<tr>
<td>Inosine Higher serum urate levels are associated with slower progression of PD. Inosine is an urate precursor that raises urate levels in blood and CSF</td>
<td>SURE-PD NCT0083690</td>
<td>II</td>
<td>Safety and tolerability study Will measure CSF urate levels in patients with early PD</td>
</tr>
<tr>
<td>Istrapadine CR Calcium antagonist</td>
<td>STEADY-PD NCT0090545</td>
<td>II</td>
<td>Safety and tolerability study UPDRS measure of disease progression</td>
</tr>
<tr>
<td>N-acetylcysteine Reduces oxidative stress as a free radical scavenger</td>
<td>NCT01470027</td>
<td>II</td>
<td>Measures of glutathione activity and clinical measures</td>
</tr>
<tr>
<td>Deferiprone An iron chelator that has been shown to reduce iron deposition in Friedreich ataxia patients. Excess iron deposition is implicated in SN toxicity</td>
<td>NCT01539837</td>
<td>II</td>
<td>Safety and tolerability study MRI measures of SN iron accumulation</td>
</tr>
<tr>
<td>Pioglitazone PPAR-gamma agonist that slows disease progression in rats and increases striatal dopamine levels</td>
<td>NCT01280123</td>
<td>II</td>
<td>Patients with early PD being recruited to this safety and tolerability study</td>
</tr>
<tr>
<td>A.W2-Neururin (CERE-120) Neurotrophic growth factor that is directly injected into the SN and putamen</td>
<td>NCT00985517</td>
<td>I/II</td>
<td>Change from baseline UPDRS III in OFF state</td>
</tr>
<tr>
<td>Cogane (PYM-50028) Oral neurotrophic factor modulator</td>
<td>NCT01060878</td>
<td>II</td>
<td>Change from baseline in UPDRS II and III in those with early and untreated PD</td>
</tr>
<tr>
<td>Early Motor IPX066 Extended-release oral formulation of carbidopa and levodopa</td>
<td>NCT01096186</td>
<td>III</td>
<td>Open label extension, to APEX-PD which showed modest improvement in UPDRS in those with early PD Side-effects included nausea and vomiting</td>
</tr>
<tr>
<td>Safinamide MAOB inhibitor, dopamine reuptake inhibitor, sodium channel antagonist and glutamate release inhibitor</td>
<td>NCT01028856</td>
<td>III</td>
<td>Extension study measuring whether safinamide delays the need to initiation of dopaminergic therapy in early PD patients</td>
</tr>
<tr>
<td>Preladenant Adenosine A2 receptor antagonist</td>
<td>NCT01155479</td>
<td>III</td>
<td>Safety and tolerability study Change from baseline in UPDRS</td>
</tr>
<tr>
<td>Advanced PD AFQ-056 Metabotropic glutamate receptor 5 antagonist (immediate release)</td>
<td>NCT01491932</td>
<td>II</td>
<td>Open label extension phase Double blind-phase showed significant benefit in the primary outcome AIMS scores</td>
</tr>
<tr>
<td>AFQ-056 Metabotropic glutamate receptor 5 antagonist (modified release)</td>
<td>NCT01491529</td>
<td>II</td>
<td>Safety and efficacy study Change from the baseline in the dyskinesia score in those with dyskinesia</td>
</tr>
<tr>
<td>IPX066 Extended-release oral formulation of carbidopa and levodopa</td>
<td>ADVANCE-PD</td>
<td>III</td>
<td>Open label extension phase recording changes in UPDRS and motor fluctuations based on home diaries. Earlier phase showed 1.1 h improvement in ON time without troublesome dyskinesia compared with immediate release levodopa Aims to show reduced OFF time compared with entacapone or placebo</td>
</tr>
<tr>
<td>BIA9-1067 Long-acting COMT inhibitor</td>
<td>BIPARK2 NCT0156073</td>
<td>III</td>
<td>Mean reduction in OFF time</td>
</tr>
<tr>
<td>Preladenant Adenosine A2 receptor antagonist</td>
<td>NCT01155466</td>
<td>III</td>
<td>Some increase in ON time increase at 24 weeks: 50 mg versus placebo 0.39 h (P = 0.008), 100 mg versus placebo 0.63 h (P = 0.005). Safety and tolerability measures also</td>
</tr>
</tbody>
</table>
Pathologically, there is extensive cortical and neocortical LB deposition which correlates with the severity of cognitive decline [40] as well as basal forebrain cholinergic neuronal loss, neurofibrillary tangles and deposition of β-amyloid, the latter occurring more often in DLB than PDD. Differentiation from AD in its early stages can be challenging and 123I-FP-CIT SPECT imaging may be helpful [41]. Symptomatic treatment remains limited to rivastigmine [42] or donepezil, which improves both cognition and behavioural features [43]. Most recently memantine has been shown to improve some neuropsychiatric features [44].

**Multiple system atrophy**

MSA manifests as severe autonomic dysfunction with cerebellar features (MSA-C), poorly levodopa-responsive Parkinsonism (MSA-P) or both [45]. The pathological hallmark is the presence of α-synuclein containing glial cytoplasmic

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**Table 2. Continued**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Trial name</th>
<th>Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>XP-21279</td>
<td>Sustained-release formulation levodopa pro-drug. Allows more time for transport across the GI tract</td>
<td>NCT01171313</td>
<td>II</td>
<td>Earlier study showed less variability in levodopa concentrations than IR carbidopa and levodopa. 60% had &gt;30% reduction in mean daily OFF time. Mean time to ON after 1st morning dose was similar</td>
</tr>
<tr>
<td>SYN115</td>
<td>Adenosine A2 receptor antagonist</td>
<td>NCT01283594</td>
<td>II/III</td>
<td>Change from the baseline in mean OFF time without troublesome dyskinesia</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Transdermal nicotine</td>
<td>NICOPARK2</td>
<td>II</td>
<td>Measuring change in UPDRS in the OFF state</td>
</tr>
<tr>
<td>A.W.hAADC-2</td>
<td>Gene coding for the enzyme that converts l-dopa to dopamine (AADC) is inserted into a non-pathogenic virus and injected into the striatum</td>
<td>NCT00229736</td>
<td>II</td>
<td>Safety study in those with mid-to-late stage PD</td>
</tr>
<tr>
<td>ProSavin</td>
<td>Intraputaminal injection of enzymes required for dopamine synthesis</td>
<td>NCT00627388</td>
<td>I/II</td>
<td>Safety and tolerability study</td>
</tr>
<tr>
<td>Gait and balance</td>
<td>Rivastigmine</td>
<td>ReSPonD</td>
<td>II</td>
<td>Recruiting patients with PD who have fallen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ISRCTN19880883</td>
<td></td>
<td>Will measure gait variability and other tasks</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Acetylcholinesterase inhibitor</td>
<td>NCT01521117</td>
<td>IV</td>
<td>Measuring changes in balance and walking</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Nicotinic receptor agonist. Improved imbalance in initial studies in patients with inherited spinocerebellar ataxia</td>
<td>Chantix-PD</td>
<td>II</td>
<td>Change in Berg Balance scale, MDS-UPDRS, mood and cognitive tests</td>
</tr>
<tr>
<td>Non-motor</td>
<td>Droxidopa Noradrenaline precursor for neurogenic orthostatic hypotension</td>
<td>NCT01176240</td>
<td>III</td>
<td>Mean change in the Orthostatic Hypotension Questionnaire composite score</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>Prostaglandin E1 derivative for constipation</td>
<td>NCT00849784</td>
<td>IV</td>
<td>Measures of change in bowel movement frequency</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Muscarinic receptor antagonist</td>
<td>URGE-PD</td>
<td>IV</td>
<td>Reduction in daily number of micturitions</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Pimavanserin SHT2A receptor antagonist</td>
<td>NCT01518309</td>
<td>III</td>
<td>Safety and efficacy studies for the treatment of PD psychosis. High placebo response with no benefit of pimavanserin. Trends towards improvement of psychosis without impairing mobility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT01050238</td>
<td></td>
<td>For those with ICDs due to DA therapy, improvement will be measured by the global impression of change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT01174004</td>
<td></td>
<td>Due to report in 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recruiting patients with mild cognitive impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MUSTARDD-PD</td>
<td>III</td>
<td>Twenty-two sites across UK aim to recruit 500 patients with early PD dementia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NCT01014858</td>
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[19].
inclusions in the central nervous system (CNS) [46]. While most cases are sporadic, polymorphisms in the SNCA gene have been identified, adding to our understanding of the pathogenesis [47]. To date, no treatments have been shown to slow the disease progression or improve survival. Riluzole, which prolongs survival in motor neuron disease (MND), did not improve survival in MSA patients in the Neuroprotection and Natural History in Parkinson Plus Syndromes study [48]. A trial of rasagline in patients with MSA-P is due to fully report later in 2012 but did not demonstrate efficacy. Potential disease-modifying therapies that have shown early promise in mice models include erythropoietin [49] and rifampicin [50]; the later reduces α-synuclein fibril formation and a human trial is underway.

Tauopathies

Tauopathies are characterised by the accumulation of hyperphosphorylated tau protein within neurons and glial cells in the CNS. Normally, tau is a soluble microtubule-associated protein found within the neuron; in the disease state the abnormally insoluble tau forms fibrillar structures of aggregated, hyperphosphorylated and ubiquinated tau with subsequent cellular toxicity. The result is a range of heterogeneous clinical syndromes with varying degrees of parkinsonism and dementia—particularly with frontal lobe involvement or an MND-like appearance [51].

Progressive supranuclear palsy

Progressive supranuclear palsy is the most common tauopathy and is characterised by abnormal deposition of four-repeat tau fibrillary tangles in neurons and glial cells within the midbrain, pallidum, thalamus and STN [51]. The classic Steele-Richardson syndrome typically presents in patients over 40 years of age with akinetic rigidity, early falls (often backwards) and supranuclear vertical gaze palsy or slowing of saccades. Other features include frontalis muscle hyperactivity giving the patient a startled expression, and a deepened voice. Neuropsychiatric disturbances such as apathy, change in social behaviour and aggression are prominent. Early impairments of cognition manifest as reduced verbal change in social behaviour and aggression are prominent. Riluzole, which prolongs survival in motor neuron disease (MND), did not improve survival in MSA patients in the Neuroprotection and Natural History in Parkinson Plus Syndromes study [48]. A trial of rasagline in patients with MSA-P is due to fully report later in 2012 but did not demonstrate efficacy. Potential disease-modifying therapies that have shown early promise in mice models include erythropoietin [49] and rifampicin [50]; the later reduces α-synuclein fibril formation and a human trial is underway.

Corticobasal degeneration

Diagnosis of CBD is challenging; it is rare, and has a variety of presentations. It may present with the classical features of corticobasal syndrome (CBS) including limb dystonia, unilateral limb apraxia, action myoclonus or cortical sensory loss; or with a more PSP-like variant with aphasia or behavioural change [56, 57]. CBS is a clinical phenotypic descriptor which may be the manifestation of a range of different pathologies including tau, Alzheimer’s disease pathology, LBs or frontotemporal lobar degeneration [57]. Pathological four-repeat tau accumulation is common to the CBD and PSP and may be present in up to half of cases of CBS [57]. Treatment is supportive; rivastigmine may improve neuropsychiatric features but with no impact upon cognition [58], and L-dopa is not helpful.

Other movement disorders

Huntington’s disease (HD) is an autosomal dominant progressive neurodegenerative disease caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntington gene on chromosome 4 [59] with severe neuronal loss in the putamen and caudate. The disease shows anticipation and the age of onset correlates inversely with the number of trinucleotide repeats. The clinical features encompass chorea, dystonia, cognitive, neuropsychiatric and metabolic disturbances and may develop between the ages of 1 and 80 years. Current treatment strategies are unsatisfactory and include the use of antidepressants and antipsychotics. Trials of striatal foetal implants are underway, as are searches for neuroprotective treatments including co-enzyme Q10. DBS has been used for disabling chorea in younger patients but experience is limited [60]. North American and European studies are ongoing in the search for reliable biomarkers for those with pre-manifest HD.

Essential tremor

Essential tremor has a prevalence of 0.4–0.9% across all age groups, rising to 4.6% in those over 65-year-old [61]. No longer labelled as ‘benign,’ the tremor often progresses and may be associated with neuropsychiatric, motor and...
functional co-morbidities [62]. Inherited in an autosomal dominant manner with reduced penetrance, no convincing loci have been identified despite exhaustive study, possibly due to considerable heterogeneity within the patient population and confounding factors such as age and co-morbid disease. Pathologically, there may be a loss of cerebellar Purkinje cells, particularly those expressing GABA_A and GABA_B receptors in the dentate nucleus of the cerebellum; brain stem LB deposition has been reported in some studies also [63]. Propanolol is established as the first-line therapy, but up to half of patients fail to respond [64]. Gabapentin and topiramate are the second-line and may work via gamma-aminobutyric acid receptor activation. Refractory cases may be considered for DBS of the ventralis intermedius nucleus of the thalamus, often with good results.

Dystonic tremor

This diagnosis has emerged with the increased use of dopamine imaging in therapeutic trials where a misdiagnosis rate of up to 15% was noted after imaging [65]. Labelled as ‘scans without evidence of dopaminergic deficit’ (SWEDDS), many of these patients demonstrated mild dystonic posturing and were thus considered to have dystonic tremor. The tremor is usually an atypical jerky rest tremor that is generally unilateral, may be focal and may display a gestic antagonist (sensory trick that reduces tremor) [66]. Available oral treatments are unsatisfactory, but botulinum toxin injection to focal muscle groups has been tried with some success.

Horizon scanning

The UK is at the forefront of movement disorder research and geriatricians are well placed to participate in this. Within England, the topic-specific NIHR-Dementias & Neurodegenerative Diseases Research Network (NIHR-DeNDReN) has a role in facilitating projects studying PD. Parkinson’s UK is a major funder of PD research in addition to providing education and support for patients and carers. Success in developing disease-modifying treatments will require the following: a better understanding of the mechanisms that underlie neuronal cell toxicity and death; the development of animal models that accurately reflect disease progression and which may be used for drug discovery programmes; and the validation of biomarkers which not only permit earlier diagnosis, but also measure disease progression and response to disease-modifying therapy. Such biomarkers are likely to be drawn from a multimodal panel of neuroimaging, blood and cerebrospinal fluid markers.

Advance care planning and palliative care

The relentless progression of most neurodegenerative movement disorders, high symptom burden and paucity of disease-modifying treatments make the requirement for a palliative approach essential. The legal framework for advance care planning (ACP) was provided by the Mental Capacity Act 2005 [67] and discussions regarding ACP can be tailored to the patient and their family with regard to their disease type and stage. Common issues include preferred place of care, antibiotic use for pulmonary infections and the use or withdrawal of artificial nutrition. Palliative care physicians are increasingly involved in the care of patients with advanced PD and other neurodegenerative diseases; unfortunately those with advanced PD are currently more likely to die in hospital than in a hospice or at home.

Conclusion

Tremendous advances have been made in the characterisation of the clinical features and underlying cellular mechanisms that underpin the movement disorders seen in older people. These advances have yet to translate into disease-modifying therapies, which will revolutionise the care these patients and are currently the focus of intense research efforts.

Acknowledgements

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Conflicts of interest

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