REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Cognitive Syndromes Associated With Movement Disorders

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CITE AS:
CONTINUUM (MINNEAP MINN) 2022;28(3, DEMENTIA):726–749.

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RELATIONSHIP DISCLOSURE:
Dr Goldman has received personal compensation in the range of $500 to $4999 for serving as an officer or member of the board of directors for the Parkinson's Foundation Scientific Advisory Board. The institution of Dr Goldman has received research/grant support from Acadia Pharmaceuticals, the American Parkinson's Disease Association, Lewy Body Dementia Association Research Center of Excellence, Michael J. Fox Foundation for Parkinson's Research, and the Parkinson's Foundation. The institution of Dr Holden has received research support from Michael J. Fox Foundation for Parkinson's Research.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Goldman and Holden discuss the unlabeled/investigational use of medications for the treatment of mood, behavioral, and cognitive symptoms, including donepezil, memantine, and rivastigmine as cognition-enhancing medications.

ABSTRACT

PURPOSE OF REVIEW: This article reviews the recognition and management of cognitive syndromes in movement disorders, including those with parkinsonism, chorea, ataxia, dystonia, and tremor.

RECENT FINDINGS: Cognitive and motor syndromes are often intertwined in neurologic disorders, including neurodegenerative diseases such as Parkinson disease, atypical parkinsonian syndromes, Huntington disease, and other movement disorders. Cognitive symptoms often affect attention, working memory, and executive and visuospatial functions preferentially, rather than language and memory, but heterogeneity can be seen in the various movement disorders. A distinct cognitive syndrome has been recognized in patients with cerebellar syndromes. Appropriate recognition and screening for cognitive changes in movement disorders may play a role in achieving accurate diagnoses and guiding patients and their families regarding progression and management decisions.

SUMMARY: In the comprehensive care of patients with movement disorders, recognition of cognitive syndromes is important. Pharmacologic treatments for the cognitive syndromes, including mild cognitive impairment and dementia, in these movement disorders lag behind the therapeutics available for motor symptoms, and more research is needed. Patient evaluation and management require a comprehensive team approach, often linking neurologists as well as neuropsychologists, psychologists, psychiatrists, social workers, and other professionals.

INTRODUCTION

Significant overlap exists between movement disorders and cognitive neurology, with many neurodegenerative conditions presenting with a mix of motor, cognitive, and behavioral signs and symptoms. Even "pure" movement disorders, such as essential tremor and dystonia, previously considered isolated motor disorders, have increasingly recognized cognitive and behavioral features.[1,2] The cognitive and behavioral features of movement disorders substantially add to disease burden and negatively affect quality of life for people living with these conditions. This clinical overlap is perhaps unsurprising, as movement and cognition are

intimately related, with coincident neuroanatomy and pathophysiology involving the cerebral cortex, basal ganglia, and cerebellum. The striatum is a key contributor in the intersection of motor function, cognition, and emotion.[3] Control of movement depends on cognitive processes, from movement plans involved in praxis to motor learning and habit formation to goal-directed actions and error detection.[4] Broader appreciation of the cognitive aspects of movement disorders with their shared neural circuitry and pathology will allow for improved diagnostic accuracy, symptom recognition, and management. This article reviews select cognitive syndromes in movement disorders as categorized by their phenomenologies: parkinsonism, chorea, ataxia, dystonia, and tremor, which are summarized in TABLE 4-1.

KEY POINTS

- Movement disorders, including dystonia and essential tremor, are increasingly recognized to have cognitive features.
- Cognitive impairment is a common feature of Parkinson disease (PD), with a lifetime risk of dementia of up to 90%.
- Bradyphrenia, or slowed thinking, is a cognitive analogue of bradykinesia, or slowed movement, in PD and may not necessarily represent cognitive decline.
- *GBA* mutation carriers have a higher risk of cognitive decline in PD.
- *LRRK2* mutation carriers have a lower risk of cognitive decline in PD.

PARKINSONISM

Parkinsonian conditions, including Parkinson disease, dementia with Lewy bodies (DLB), multiple system atrophy, progressive supranuclear palsy, and corticobasal syndrome, are connected by shared motoric features that may include bradykinesia (slowed movement), rigidity, tremor, gait impairment, and postural instability.

Parkinson Disease

Cognitive impairment is one of the most common nonmotor symptoms in Parkinson disease (PD). The cumulative prevalence of dementia in people with PD is 75% to 90%.[5] Cognitive symptoms can occur at any stage of PD, with 20% to 30% of patients already meeting criteria for mild cognitive impairment (MCI) at the time of diagnosis.[6] Furthermore, bradyphrenia, or slowed thinking, is a cognitive analogue of bradykinesia in PD and may not necessarily represent cognitive decline. The criteria for MCI in PD (PD-MCI) published in 2012 are shown in TABLE 4-2.[7-9] Considered a transitional stage between normal cognition and dementia, PD-MCI transitions to PD dementia at a rate of approximately 10% to 15% annually, although some patients remain stable at an MCI stage and some may even revert to normal cognition on serial examinations.[10]

Clinical predictors of PD dementia include older age, male sex, and greater motor symptom severity, presence of hallucinations, rapid eye movement (REM) sleep behavior disorder, and vascular risk factors (eg, hypertension, smoking).[11] The genetics of PD also play a role in dementia risk, with overlap among PD, Alzheimer disease (AD), and Lewy body dementia genetic risk profiles. This overlap is only partially explained by known disease-causing and risk-factor genes, including *SNCA*, *GBA*, and *APOE* ε4.[12] *GBA* mutations are the most common genetic risk factor for PD, with 5% to 15% of patients with PD carrying mutations, and are more commonly found in those of Ashkenazi Jewish descent.[13] *GBA* carriers may be more likely to experience nonmotor symptoms of PD, affecting olfaction, mood, autonomic function, and cognition.[14,15] Mutations in *LRRK2* are the most common known cause of monogenic PD (5% to 7% of familial PD cases) and may be associated with a lower risk of cognitive impairment than other genetic forms of PD.[16,17] The H1 haplotype of *MAPT,* a gene more commonly associated with frontotemporal dementia, has been implicated in the risk of dementia in PD.[18,19] Genetic counseling and testing may be considered for PD, particularly those with a young onset (younger than 50 years) and family history of PD.

Diagnostic criteria for PD dementia require impairment in at least two cognitive domains, along with functional impairments in daily living that cannot

be ascribed to motor deficits or autonomic symptoms.[20] Distinguishing functional impairment due to cognitive symptoms from that due to motor deficits can be difficult and often requires a thorough interview with the patient and a knowledgeable informant; PD-specific questionnaires and performance-based measures of functional abilities related to cognition have also been used in PD.[21-24] The point prevalence is 24% to 31%, and the cumulative incidence is about 50% at 10 years for dementia in PD.[25,26] PD dementia has a heterogeneous profile, but executive and visuospatial dysfunction are frequent, and variable impairments in memory and attention may occur. This cognitive profile can help distinguish PD dementia from Alzheimer disease (TABLE 4-3). Related to dopaminergic dysfunction in frontostriatal networks, executive

TABLE 4-1 **Movement Disorders Associated With Cognitive Features**

Movement disorder	Movement features	Cognitive features	Structural brain MRI findings
Parkinsonism			
Parkinson disease	Bradykinesia, rigidity, resting tremor	Bradyphrenia, executive and visuospatial dysfunction	None specific but may have cerebral atrophy, especially in setting of dementia
Dementia with Lewy bodies	Bradykinesia, rigidity; typically less resting tremor	Executive and visuospatial dysfunction, cognitive fluctuations	Relative preservation of medial temporal lobe compared to Alzheimer disease
Multiple system atrophy	Parkinsonism, cerebellar ataxia	Subtle changes in executive and visuospatial function	Hot cross bun sign in pons, hyperintense putaminal rim on T2-weighted images
Progressive supranuclear palsy	Parkinsonism, early and frequent falls, vertical gaze palsy	Executive dysfunction, impaired verbal fluency	Hummingbird sign: reduced midbrain to pons ratio
Corticobasal syndrome	Parkinsonism, apraxia, dystonia, myoclonus, alien limb	Executive dysfunction, impaired social cognition, neglect, aphasia	Asymmetric parietal atrophy
Chorea			
Huntington disease	Chorea	Psychomotor slowing, executive dysfunction, poor free recall, impaired emotion processing	Caudate atrophy
Chorea-acanthocytosis	Chorea, dystonia, tongue protrusion with eating	Executive, memory, and visuospatial dysfunction	Caudate head atrophy
Wilson disease	Choreoathetosis, tremor, dystonia	Slowed processing speed, executive dysfunction	T2 hyperintensities in putamen, globus pallidus, and thalamus
Dentatorubral-pallidoluysian atrophy	Choreoathetosis, myoclonus, ataxia	Executive dysfunction, psychomotor slowing, mild memory deficits	T2 hyperintensities in subcortical white matter and thalamus, atrophy of cerebellum and pontine tegmentum

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dysfunction includes impairments in planning, multitasking, and attentional set shifting. Impairments in memory and visuospatial function may be partly related to decreased attention and executive dysfunction, causing poor organization and planning in testing responses, as well as poor memory retrieval. Patients may provide more accurate responses to recognition tasks than to free recall. Language is relatively spared in PD dementia, but impairment in sentence comprehension and verbal fluency (lexical and semantic) can be seen; reduced semantic fluency may be associated with the conversion from PD-MCI to PD dementia.[27] Visuospatial and language dysfunction may be more related to cortical pathology, including Lewy body deposition and AD copathology. Therefore, these cognitive features are associated with a

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Movement disorder	Movement features	Cognitive features	Structural brain MRI findings
Pantothenate kinase-associated neurodegeneration	Choreoathetosis	Impaired executive function, processing speed, and attention	Eye of the tiger sign
Aceruloplasminemia	Chorea, parkinsonism, tremor, dystonia	Executive dysfunction, impulsivity, perseveration, cognitive slowing, and apathy	T2 hypointensities of basal ganglia nuclei
Ataxia			
Fragile X-associated tremor/ataxia syndrome	Ataxia, tremor, parkinsonism	Global impairments, with more executive and verbal fluency impairment	Middle cerebellar peduncle sign
Spinocerebellar ataxias	Ataxia, abnormal eye movements, dysarthria	Executive dysfunction, verbal memory impairment	Cerebellar atrophy; may have extracerebellar atrophy depending on type of spinocerebellar atrophy
Friedreich ataxia	Ataxia, spasticity, areflexia	Slowed processing, impaired conceptual thinking, impulsivity	Thinning of cervical cord, cerebellar atrophy
Niemann-Pick Type C	Ataxia, dystonia, vertical gaze palsy, dysarthria	Executive and visuospatial dysfunction, preserved verbal memory, obsessive-compulsive tendencies	Frontal and cerebellar atrophy, T2 hyperintensities in parietooccipital white matter, reduced midbrain to pons ratio (not as severe as in progressive supranuclear palsy)
Other			
Dystonia	Abnormal muscle contraction, fixed postures	Mild executive and attentional impairments, impaired social cognition	None specific
Essential tremor	Postural and action tremor	Mild impairments in attention, verbal fluency, executive and visuospatial function	None specific

MRI = magnetic resonance imaging.

higher risk of progression to PD dementia.[28] To date, the diagnosis of PD dementia is based on clinical criteria, although interest is growing in biomarkers (eg, CSF, MRI, nuclear imaging, EEG) associated with PD dementia that may have potential for future incorporation into diagnostic criteria. From a clinical perspective, studies such as structural MRI, EEG, laboratory tests (eg, vitamin B_{12}, thyroid-stimulating hormone [TSH]) are more often used to exclude other cognitive syndromes rather than diagnose PD dementia per se.

TABLE 4-2 **Diagnostic Criteria for Mild Cognitive Impairment in Parkinson Disease[a]**

I Inclusion criteria

- **A** Diagnosis of Parkinson disease (PD)
- **B** Gradual cognitive decline, in the context of established PD, either reported by the patient or informant or observed by the clinician
- **C** Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (refer to Section III)
- **D** Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II Exclusion criteria

- **A** Diagnosis of PD dementia
- **B** Other primary explanation for cognitive impairment (eg, delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- **C** Other PD-associated comorbid conditions (eg, motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III Specific guidelines for mild cognitive impairment in PD (PD-MCI) Level I and Level II categories[b]

- **A** Level I (abbreviated assessment)[b]
  - **1** Impairment on a scale of global cognitive abilities validated in PD[c,d] *OR*
  - **2** Impairment on at least two cognitive tests in a limited cognitive battery (ie, battery includes less than two tests within each of the five cognitive domains or less than five cognitive domains are assessed)[c]
- **B** Level II (comprehensive assessment)[b]
  - **1** Neuropsychological testing that includes at least two tests in each of the five cognitive domains (ie, attention/working memory, executive, language, memory, and visuospatial)
  - **2** Impairment on at least two tests (two in one domain or one in each of two domains)[c]

[a] Data from Litvan I, et al, Mov Disord.[7]

[b] Level II criteria allow for a more comprehensive diagnosis of PD-MCI, including cognitive subtyping. Level I, however, is considered adequate for diagnosing PD-MCI, particularly for clinicians with limited access to formal neuropsychological testing, and both Level I and Level II criteria predict the risk of developing PD dementia in longitudinal studies

[c] Impairment is defined as:

- Performance 1 to 2 standard deviations below appropriate norms, *OR*
- Significant decline demonstrated on serial cognitive testing, *OR*
- Significant decline from estimated premorbid levels

[d] Global cognition screening test examples: Montreal Cognitive Assessment (MoCA),[8] Parkinson Disease-Cognitive Rating Scale [PD-CRS].[9]

Within the broader scope of neuropsychiatric symptoms of PD, cognitive impairment can be comorbid with behavioral and mood syndromes, including apathy, psychosis, anxiety, depression, and impulse control disorders.[29] These neuropsychiatric symptoms can manifest even at mild stages of cognitive impairment, exacerbating one another and complicating the clinical picture of PD, necessitating regular symptomatic screening, delineation of contributing

Distinguishing Features of Parkinsonian Dementias and Alzheimer Disease TABLE 4-3

Feature	Parkinson disease dementia	Dementia with Lewy bodies	Alzheimer disease dementia
Dementia onset	Usually later, >1 year after motor features	Earlier, <1 year after motor symptoms or prior	Early
Prominent cognitive symptoms	Attention, executive function, visuospatial function	Attention, executive function, visuospatial function	Memory, language
Parkinsonism	Yes	Maybe; resting tremor less frequent	Rarely
Visual hallucinations	Possible	Common	Rarely
Fluctuation of cognitive impairment	Possible	Common	Rarely
Rapid eye movement (REM) sleep behavior disorder	Common	Common	Rarely
Average duration from cognitive symptom onset to death	5-7 years	5-7 years	7-10 years
Neuroimaging			
Structural	Can be normal; relative maintenance of medial temporal volumes	Diffuse cortical atrophy; white matter hyperintensities in temporal lobes; relative maintenance of medial temporal volumes	Medial temporal and parietal atrophy
Molecular	Fludeoxyglucose positron emission tomography (FDG-PET): posterior hypometabolism Dopamine transporter scan: abnormal	FDG-PET: posterior hypometabolism Dopamine transporter scan: abnormal	FDG-PET: temporal and parietal hypometabolism Dopamine transporter scan: normal
Neuropathology	Lewy body/α-synuclein pathology in cortex, limbic, and brainstem; more severe nigral cell loss; about 30% Alzheimer disease (AD) copathology	Lewy body/α-synuclein pathology in cortex and limbic structures, more severe in hippocampus than Parkinson disease (PD) dementia; about 80% AD copathology; higher amyloid-β and tau load in cortex and striatum than PD dementia	Extracellular amyloid-β 42 plaques; intracellular hyperphosphorylated tau neurofibrillary tangles; vascular amyloid deposition; granulovacuolar degeneration

factors, and appropriate management. Some neuropsychiatric symptoms, such as psychosis, apathy, and excessive daytime sleepiness, may be more prominent as the disease progresses.

Dementia With Lewy Bodies

DLB is the second most common neurodegenerative dementia after AD, accounting for up to 30% of dementia cases.[30] Copathology between DLB and AD is also common, with up to 80% of clinical DLB cases demonstrating AD pathology on autopsy.[19] In contrast, only approximately 30% of PD dementia cases have AD copathology.[30-32] In the presence of AD copathology, DLB may present with less prominent core clinical features, and, thus, may render an accurate and timely diagnosis of DLB more challenging.[33] Updated in 2017, DLB criteria include a dementia syndrome with objective cognitive deficits and functional impairment and four core clinical features: parkinsonism, REM sleep behavior disorder, visual hallucinations, and cognitive fluctuations.[34] The DLB criteria also include two categories for biomarkers: (1) indicative biomarkers: reduced dopamine transporter uptake in basal ganglia by single-photon emission computed tomography (SPECT) or positron emission tomography (PET), abnormal low uptake on ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy, or polysomnographic confirmation of REM sleep without atonia; and (2) supportive biomarkers: relative preservation of medial temporal lobe structures on CT/MRI scans, generalized low uptake on SPECT/PET with reduced occipital activity with or without the cingulate island sign on fludeoxyglucose positron emission tomography (FDG-PET), or prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range. Research criteria have been published for earlier stages of a DLB process, termed *prodromal DLB*.[35] Three subtypes of prodromal DLB have been proposed: (1) MCI due to Lewy bodies, (2) delirium onset, and (3) psychiatric onset. These criteria require further study and operationalization in clinical settings, particularly for the delirium- and psychiatric-onset presentations of prodromal DLB. Of note, nonamnestic presentations of MCI seldom progress to clinical AD, but they are more likely to progress to DLB, with a risk 10 times higher than that of amnestic MCI.[36]

An area of diagnostic and terminological quandary lies in distinguishing PD dementia and DLB, especially as clinical features overlap; both diagnoses fall under the umbrella term *Lewy body dementia*. Visual hallucinations and cognitive fluctuations can occur in either PD dementia or DLB, although they are more frequent and prominent in DLB, occurring even in the earliest stages of the condition. The primary clinical distinguishing factor between the two conditions is timing of symptom onset, referred to as the *1-year rule*: PD dementia is diagnosed if motor symptoms have been present for at least 1 year before the onset of cognitive symptoms; DLB is diagnosed if the onset of motor and cognitive symptoms is concurrent or if cognitive symptoms predate motor symptoms (CASE 4-1).[34] Some question remains regarding whether PD dementia and DLB are truly separate conditions or represent a disease spectrum. Clinical trials of cognitive-enhancing therapies may include participants with either PD dementia or DLB in the study design, although it is uncertain whether responses to interventions differ by diagnosis.[37,38] In clinical practice, the conditions are easier to distinguish earlier in the disease course, but they can look similar in later stages, with similar cognitive profiles of executive and visuospatial dysfunction,

behavioral symptoms, and autonomic dysfunction. A practical way to distinguish PD dementia from DLB is based on the relative prominence of cognitive versus motor symptoms, particularly at onset, that is, to determine what symptoms led the patient to seek medical care.

Atypical Parkinsonian Syndromes

Atypical parkinsonian syndromes include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS). Cognition is affected in all atypical parkinsonian syndromes to varying degrees, even at their earliest stages. Executive dysfunction is the most common cognitive manifestation, although some studies suggest unique cognitive features in these parkinsonian conditions.[39]

MSA is classified as a synucleinopathy, along with PD and DLB, characterized by variable combinations of parkinsonism, cerebellar ataxia, and severe autonomic dysfunction. Dementia has previously been considered a nonsupportive feature of MSA by diagnostic criteria, although some degree of cognitive impairment is present in 22% to 37% of neuropathologically proven cases.[40,41] Furthermore, DLB is the most common clinical misdiagnosis made in pathologically proven MSA. Cognitive deficits are qualitatively similar in MSA and DLB/PD dementia, although less severe overall in MSA. Neuropsychological testing may be required for detection, as cognitive screening tests could miss more subtle changes in MSA.[42,43]

PSP and CBS are tauopathies rather than synucleinopathies; as such, clinical and neuropathologic overlap with frontotemporal dementia syndromes can be seen. Genetic causes of frontotemporal dementia, including *C9orf72*, *GRN*, and *MAPT*, should be considered in these overlap cases. Up to 70% of people with PSP will develop dementia during the course of their disease, with 10% initially presenting for evaluation of primarily cognitive symptoms.[44] Along with the core motor features of PSP (postural instability, akinesia, axial rigidity, and restriction of vertical gaze), executive dysfunction is common, although impairments in memory, language, visuospatial function, and social cognition can be seen. The Frontal Assessment Battery may be more sensitive for cognitive screening of patients with PSP than the Montreal Cognitive Assessment (MoCA) or Mini-Mental Status Examination (MMSE).[45,46] Verbal fluency, both lexical and semantic, is particularly impaired in PSP; production of seven or fewer words per minute can help distinguish PSP from PD with 85% specificity and sensitivity.[47] Lexical fluency is generally more impaired in PSP than semantic fluency, in contrast to what is typically seen in AD.[48] Overlap with nonfluent/agrammatic primary progressive aphasia can occur in PSP, as well as with CBS. PSP is now recognized with multiple variants beyond the classic Richardson syndrome, highlighting the clinical constellation of movement, cognitive, language, and behavioral phenotypes.[49]

CBS can be caused by underlying corticobasal degeneration pathologically, but it can also be caused by PSP, frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43), or AD pathologies. Presenting clinically as a mixture of limb apraxia, parkinsonism, dystonia, myoclonus, and alien limb phenomenon, CBS is the most asymmetric of the parkinsonian disorders.[50] Asymmetric parietal atrophy on neuroimaging is often present. Executive dysfunction may be seen, but more prominent language, visuospatial, and social cognition (ie, effects of interpersonal and affective factors on cognitive processes; one example in parkinsonian conditions includes the expression and

KEY POINTS

- Executive, attentional, and visuospatial dysfunction are more common in PD compared with the more amnestic deficits seen in Alzheimer disease (AD).
- Copathology with AD is very common in dementia with Lewy bodies and can dampen the expression of core clinical features.
- Core clinical features of dementia with Lewy bodies include parkinsonism, visual hallucinations, rapid eye movement (REM) sleep behavior disorder, and cognitive fluctuations.
- No clinical criteria yet exist for a mild cognitive impairment stage of dementia with Lewy bodies, although nonamnestic mild cognitive impairment with any core clinical features should raise suspicion for prodromal dementia with Lewy bodies.
- All core clinical features of dementia with Lewy bodies can also be seen in PD dementia, although at lower frequencies overall.
- The main differentiating factor between PD dementia and dementia with Lewy bodies is timing of symptom onset: what came first, motor or cognitive symptoms?
- PD dementia and dementia with Lewy bodies may be on a clinical and pathologic spectrum rather than completely separate diagnostic entities.
- It is important to delve into examples of the patient's "memory trouble," as the affected cognitive domain may not be memory at all.

recognition of facial emotions[51]) deficits may help distinguish CBS. Parietal lobe dysfunction is prominent overall, with potential spatial or visual neglect, impaired praxis, Balint syndrome (ocular ataxia, oculomotor apraxia, and simultanagnosia), Gerstmann syndrome (left-right confusion, finger agnosia, acalculia, and agraphia), and cortical sensory changes. Up to one-third of patients with CBS display language dysfunction, which may be the presenting symptom, with prevalence increasing with disease duration.[52] Word-finding difficulty, impaired repetition, agraphia, and apraxia of speech can occur.

Management of Cognitive Features in Parkinsonian Conditions

Management of cognitive syndromes in parkinsonian disorders may include pharmacologic, nonpharmacologic, and psychosocial strategies. First, potential contributing factors, such as medication side effects and comorbid conditions (eg, sleep disorders, orthostatic hypotension, depression) should be evaluated

CASE 4-1

A 68-year-old man, accompanied by his wife of 40 years, presented to the neurology clinic for an initial evaluation of "memory trouble" over the past 3 to 4 years. He noted that he had been increasingly forgetful over this time. He and his wife shared that he had difficulty following a recipe and lost track of the steps he should take. He had limited his driving because he nearly collided with a stopped car in front of him at a stoplight, misjudging its distance from his car. His wife recently took over managing their finances. He noted slowness in his golf game and while walking the course in the past few months. He described his sleep as "good," although his wife complained that "he never stops moving around and mumbling all night," disrupting her sleep for at least the past 10 to 15 years. They denied any hallucinations or delusions, mood changes, or significant fluctuations in his alertness or attention. He was not taking any medications for these cognitive or motor symptoms. He had a history of hypertension controlled with medications, and he had no family history of dementia or parkinsonism.

On examination, mental status testing showed a Montreal Cognitive Assessment (MoCA) score of 22/30, with points lost for the trail-making component, figure copy, clock hand placement, and serial subtractions, and delayed recall of 2/5, which improved to 4/5 with cueing. He had mild bradykinesia and rigidity in his upper and lower extremities, right worse than left side, with decreased right arm swing and shortened stride length. He did not have resting tremor or postural instability.

The clinician noted that the examples of cognitive changes he and his wife mentioned were more consistent with difficulty with organizational skills and decision making. Formal neuropsychological testing revealed moderate impairment on tests of attention, working memory, executive function; mild visuospatial deficits and difficulty with word list and story recall; intact naming and language abilities; and no significant depression or anxiety. Brain MRI revealed moderate cerebral volume loss and mild ischemic changes but no clear medial temporal lobe atrophy.

and treated. At present, only one medication, rivastigmine, has been approved by the US Food and Drug Administration (FDA) and European Union regulatory bodies for the treatment of PD dementia, and donepezil is approved in Japan for DLB. However, several pharmacologic treatment trials and related meta-analyses have been conducted for PD-MCI, PD dementia, and DLB,[53,54] mainly using medications developed for AD, including cholinesterase inhibitors and memantine. With some evidence of benefit, especially for rivastigmine and donepezil, these medications may be trialed with appropriate counseling and monitoring for potential side effects of nausea, gastrointestinal upset, bradycardia, and syncope.[55] The transdermal patch form of rivastigmine may limit gastrointestinal side effects in some patients, but skin reactions may occur in some. Furthermore, even without significantly noticeable improvement in cognition, cholinesterase inhibitors can be continued; sudden discontinuation may be associated with worsening of cognition and associated behavioral

COMMENT

This case presents an overlap of cognitive and movement signs and symptoms, although the patient's chief complaint is "memory trouble." Movement symptoms were elicited through history-taking and confirmed with neurologic examination. Parkinsonian features can often be attributed to "just getting older" or musculoskeletal issues, such as "frozen shoulder," by patients. This case highlights the importance of delving into examples of the patient's "memory trouble," as the affected cognitive domain may not have been memory at all; rather, this patient's symptoms were more consistent with executive dysfunction and visuospatial impairment. He exhibited functional impairments related to paying bills, cooking, and driving. His bedside screening and neuropsychological evaluation indicated that he would meet classification for dementia (major neurocognitive disorder) at that point.

His dementia, along with concomitant parkinsonism and rapid eye movement (REM) sleep behavior disorder, indicates an underlying synucleinopathy, namely dementia with Lewy bodies (DLB). This case illustrates the importance of identifying the chronology of cognitive and motor symptoms to help with differential diagnosis, particularly when considering Lewy body disorders. It can be difficult to apply the "1-year rule" discriminating Parkinson disease from DLB in cases in which recall of the timing of symptom onset may not be reliable and no previous neurologic examination is documented. Had he presented while in mild cognitive impairment stages before his functional decline, mild cognitive impairment due to Lewy bodies would be considered, with monitoring for progression to DLB.

symptoms in Lewy body dementia.[53,56] Several novel agents are being tested in PD dementia and DLB, including a D1 positive allosteric modulator (mevidalen) and a p38 alpha kinase inhibitor (neflamapimod), among others.[55]

Pharmacologic treatments for cognition in MSA, PSP, and CBS are less well studied, and no medications for this indication have been approved by regulatory bodies. Trials of cholinesterase inhibitors and memantine in frontotemporal dementia may provide considerations for PSP and CBS, but some studies suggest worsened motor and behavioral features in these conditions.[57] Further attention is needed to understand how cognitive treatments can impact motor and behavioral symptoms in atypical parkinsonian syndromes.[58]

Deep brain stimulation for cognitive symptoms in PD dementia and AD has begun to be explored with the nucleus basalis of Meynert, which has widespread cholinergic projections, as a target.[59] Although the surgery and ensuing low-frequency stimulation were well tolerated in six patients with PD dementia, no changes in cognitive measures were seen at 6 weeks. Noninvasive brain stimulation, including transcranial magnetic stimulation and transcranial direct current stimulation, also has been investigated in PD cognitive impairment without clear beneficial effect thus far.[60-62]

The importance of risk factor modification and a brain-healthy lifestyle should also be stressed in parkinsonian conditions, including regular physical and aerobic exercise, cognitively stimulating activities, and optimal management of cardiovascular risk factors.[63] Safety screenings regarding driving, firearms, and work and home environments should regularly occur. Screening for and managing caregiver distress is also important because cognitive impairment contributes to caregiving burden and nursing home placement.[64,65]

CHOREA

Chorea is a hyperkinetic movement, and its phenomenology often includes involuntary, irregular, flowing movements that can involve the extremities, face, and trunk. Chorea can be due to neurodegenerative conditions, such as Huntington disease, or secondary causes such as stroke, metabolic derangements, or autoimmune conditions.

Huntington Disease

Huntington disease (HD) is an autosomal dominant neurodegenerative condition caused by CAG repeat expansion in the *HTT* gene on chromosome 4. The average age of onset is 40 years, although it has broad variation depending on the length of the repeat expansion. The clinical triad of HD includes movement, cognitive, and psychiatric manifestations, with potential clinical onset in any of those symptomatic categories: 51.8% of patients present with all three and 25% with movement and cognitive, 14.3% with movement and psychiatric, and 8.9% with isolated movement manifestations.[66]

Neuropsychiatric symptoms (eg, apathy, irritability, and executive dysfunction) are common in premanifest stages of HD.[67] Adults with HD can have chorea but also parkinsonian and/or dystonic features, although the latter features occur more commonly in juvenile HD. Neuropathologically, the caudate and putamen are most severely affected, but cortical volume loss in regions receiving projections from the striatum (dorsolateral frontal and orbitofrontal) and altered white matter connectivity among brain regions involved in cognitive and motor processes can also occur.[68,69]

On neuropsychological testing, patients with HD display prominent deficits in psychomotor and executive skills, memory, emotion recognition, and social cognition.[69,70] Psychomotor slowing is one of the earliest and best predictors of disease progression, which can be demonstrated on timed tasks such as the Stroop Color and Work Test, Symbol Digit Modalities Test, and Trail Making Test.[71] These impairments affect functional independence, including tasks such as driving, working, and managing finances. Impairment can also be seen on executive function, verbal fluency, and attention tasks. For memory in HD, free recall is often impaired, with higher rates of recall errors, with relatively intact cued recall and recognition memory.[70] People with HD may have difficulty processing emotional facial expressions, particularly negative emotions, which can manifest early in the disease course and impact interpersonal relationships, empathy, and adherence to social norms.[72] Other aspects of social cognition, including theory of mind, with difficulty interpreting the beliefs, mental states, and intentions of others, may be affected.[73] Cognitive domains that are less dependent on subcortical regions are usually preserved in HD (ie, semantic memory, language, visuospatial function, and orientation).[69] The Unified Huntington's Disease Rating Scale contains three brief cognitive tasks, all timed, which can be helpful in screening for HD-specific cognitive changes: verbal fluency, Symbol Digit Modalities Test, and the Stroop Task.[74]

Several small treatment trials for cognition in HD have been conducted, all without demonstrated benefit.[75-77] Cholinesterase inhibitors, including donepezil and rivastigmine, have not elicited significant cognitive improvement in HD, although they have introduced no significant adverse effects.[78,79] Memantine has been studied in a small open-label trial with no benefit for cognition seen at 3 months.[76] Patients with HD should be regularly screened regarding home safety and driving; about half of patients with HD who are active drivers fail a formal driving evaluation.[80] Genetic counselors play an important role in the diagnosis and management of HD. In addition, like many of the cognitive-movement syndromes described, a multidisciplinary approach with neurologists, psychiatrists, psychologists, social workers, and other health care specialties is helpful to patients and their families.

Chorea-acanthocytosis

Chorea-acanthocytosis is a rare, autosomal recessive condition due to mutations in the *VPS13A* gene, which codes for the protein chorein. Chorea-acanthocytosis can clinically mimic HD, although it typically presents with seizures first, followed by chorea and dystonia; characteristic tongue protrusion while eating occurs.[81] The average age of onset is between 25 and 45 years. Similar to cognitive deficits seen in HD, impairments in chorea-acanthocytosis are primarily dysexecutive. Memory and visuospatial impairment can occur, although likely secondary to underlying frontosubcortical dementia.[82,83]

Neuroimaging findings include striatal atrophy, especially the caudate head, which thereby reinforces the brain-behavior link of dysexecutive syndromes and frontostriatal circuitry.

Wilson Disease

Wilson disease, an autosomal recessive condition due to mutation in the *ATP7B* gene coding for a copper transport protein, manifests with varied clinical

KEY POINTS

- Cognitive impairment can occur in all atypical parkinsonian conditions, although typically more prominently in progressive supranuclear palsy and corticobasal syndrome than in multiple system atrophy.
- With clinical overlap of parkinsonism, behavior/personality changes, and/or primary progressive aphasia, consider testing for frontotemporal dementia genes: *C9orf72*, *GRN*, and *MAPT*.
- Lexical fluency impairment can help distinguish progressive supranuclear palsy from other conditions, including PD and AD.
- Corticobasal syndrome is the most asymmetric of the parkinsonian disorders.
- Side effects of cholinesterase inhibitors include gastrointestinal symptoms, bradycardia, hypotension, and syncope.
- Sudden discontinuation of cholinesterase inhibitors can cause abrupt cognitive decline in PD dementia and dementia with Lewy bodies.
- Depression, apathy, and irritability are common in Huntington disease and can occur at any stage of disease, including before the onset of motor symptoms.
- Cognitive, behavioral, and motor features are highly intertwined in Huntington disease and highlight the involvement of both striatal/subcortical and cortical pathologies.

presentations.[84] This mutation leads to deposition of copper in multiple organ systems, namely the central nervous system, eyes, and liver. Within the central nervous system, the putamen and the pallidum are most affected, leading to movement manifestations of choreoathetosis, tremor, and/or dystonia. Cognitively, people with Wilson disease can display slowed processing speed and executive dysfunction, with verbal and visual memory less affected. The cognitive changes in Wilson disease are most pronounced in those with greater brain MRI changes, commonly featuring T2 hyperintensities in the lenticular nuclei, ventrolateral thalamus, and hypothalamus.[85]

Dentatorubral-pallidoluysian Atrophy

Dentatorubral-pallidoluysian atrophy (DRPLA) is an autosomal dominant condition caused by a CAG repeat expansion in the *ATN1* gene; its prevalence is higher in Japan than in other countries.[86] Onset is typically around the age of 30 years but ranges from infancy to midadulthood. Common signs and symptoms include seizures, choreoathetosis, myoclonus, and/or ataxia, as well as early-onset dementia and psychiatric symptoms of mood instability, apathy, psychosis, and childlike behavior. Differential diagnoses in adults with chorea, ataxia, and dementia include spinocerebellar ataxias (SCAs) including type 17 (SCA17) (refer to the section on spinocerebellar ataxia below), HD, HD-like 1, and HD-like 2. In children, in addition to seizures, behavioral changes, and myoclonus, progressive intellectual deterioration may occur. Typical cognitive deficits include psychomotor slowing, executive dysfunction, and mild memory deficits. CAG repeat size correlates with the severity of cognitive and psychiatric symptoms.[87] Neuropathologically, degeneration of the dentatorubral and pallidoluysian systems occurs with intranuclear inclusions on histopathology.

Neurodegeneration With Brain Iron Accumulation

The neurodegeneration with brain iron accumulation (NBIA) conditions are rare genetic movement disorders, with variable phenomenologies, including chorea, parkinsonism, tremor, and/or dystonia, and are caused by iron accumulation in the brain. NBIA conditions are recognized to include multiple different gene mutations.[88] In the classic form of pantothenate kinase–associated neurodegeneration (PKAN), an autosomal recessive disorder due to *PANK2* gene mutations, a severe rapidly progressive choreoathetosis occurs in the first decade of life. An atypical form also exists with a less severe, more slowly progressive movement disorder in the second to third decade of life. Both display the pathognomonic eye of the tiger sign on neuroimaging with T2-weighted brain MRI sequences. Patients with PKAN can have a subcortical dementia with impaired executive function, processing speed, and attention. In some cases, cognitive symptoms can precede motor features.[89]

Aceruloplasminemia is another NBIA with potential cognitive manifestations due to a mutation in the ceruloplasmin (*CP*) gene, leading to iron deposition in the brain in the absence of ceruloplasmin ferroxidase activity. Aceruloplasminemia can present with chorea, parkinsonism, tremor, and/or dystonia, typically in the fifth to sixth decades of life. Cognitive impairment is the presenting symptom in up to 50% of patients, typically manifesting as a subcortical dementia with executive dysfunction, impulsivity, perseveration, cognitive slowing, and prominent apathy.[90]

ATAXIA

Impaired coordination of voluntary movements is most obviously appreciated in ataxic cerebellar conditions, but impairments are also seen in the coordination of thought and behavior in cerebellar disorders.

Cerebellar Cognitive Affective Syndrome

The cerebellum was long considered solely in relation to motor control, with symptoms of ataxia, dysmetria, dysarthria, and oculomotor abnormalities. The cerebellum's role in cognition and behavior is increasingly appreciated since the description of the cerebellar cognitive affective syndrome by Schmahmann and Sherman[91] in 1998. Conceptualized as "dysmetria of thought," cerebellar cognitive affective syndrome is caused by impairment of the cerebellar regulation of the speed, stability, and appropriateness of cognitive processes.[92] Just as the cerebellum modulates the precision and accuracy of movements, so too does it regulate cognition and behavior. The posterior lobe of the cerebellum is most involved in cognitive and limbic networks; damage to this region (structural lesions such as stroke, hemorrhage, or tumor or neurodegeneration) results in cerebellar cognitive affective syndrome. Cognitively, deficits in executive and visuospatial function occur, as well as in language, attention, and regulation of affect. The affective deficits can present as autism spectrum features with impaired social skills and communication abilities.[93] Perseveration, disinhibition, poor verbal fluency, and impaired prosody may be present.[91,92] A cerebellar cognitive affective syndrome–specific scale has been developed, targeting these specific domains of impairment, and is more sensitive than the MMSE or MoCA.[94] Features of cerebellar cognitive affective syndrome can be present in the cerebellar movement disorders.

Fragile X-Associated Tremor/Ataxia Syndrome

Fragile X syndrome is the most common inherited form of intellectual and developmental disabilities, related to CGG repeat expansion (greater than 200 repeats) in the *FMR1* gene on the X chromosome. Premutation repeat lengths between 55 and 199 repeats are associated with ataxia, tremor, parkinsonism, autonomic dysfunction, and cognitive impairment, termed *fragile X-associated tremor/ataxia syndrome* (FXTAS) (CASE 4-2). The average age of onset of FXTAS is in the sixties, usually with an action tremor followed by some degree of ataxia, although clinical presentations can be variable. Screening for the *FMR1* premutation should be considered for patients with atypical parkinsonian syndromes and dementia. Brain MRI may reveal T2 hyperintensities of the middle cerebellar peduncles, present in 60% of affected men and 13% of affected women.[95] Symptoms and signs are generally less severe in women than men, related to X-inactivation. Clues within the family history include grandsons with intellectual disability or autism spectrum disorder and/or daughters with premature ovarian failure. Repeat expansion size is associated with severity of cognitive impairment, particularly for repeats greater than 70.[96,97] Cognition can be globally impaired in FXTAS, although it more often presents as executive dysfunction and impaired verbal fluency with features of a mixed cortical-subcortical dementia.[98,99] Even for patients with FXTAS but who do not have personal cognitive concerns, neuropsychological testing shows worse cognitive scores on overall IQ and logical memory tests than their noncarrier siblings.[97] However, no differences were seen on executive function tasks.[97]

KEY POINTS

- Psychomotor slowing is one of the earliest and best predictors of Huntington disease progression, which can be demonstrated on timed tasks such as the Stroop Color and Work Test, Symbol Digit Modalities Test, and Trail Making Test.
- It is important to screen patients with Huntington disease for behavioral symptoms because they can affect daily function, safety, and performance on cognitive tests.
- Genetic counselors play important roles in the diagnosis and management of Huntington disease. In addition, like many of the cognitive-movement syndromes described, a multidisciplinary approach with neurologists, psychiatrists, psychologists, social workers, and other health care specialties is helpful to patients and their families.
- In addition to motor features, cerebellar disorders may present with cognitive dysfunction.
- Evidence for the cerebellar cognitive affective syndrome comes from studies of patients with cerebellar lesions, including strokes and neurodegenerative conditions.
- The cerebellar cognitive affective syndrome includes impairment in processing speed, working memory, executive function, visuospatial function, language, and attention.
- The cerebellum may play a role in emotional and affective regulation.

Spinocerebellar Ataxia

The list of known SCAs with genetic mutations continues to grow, with 40 genetic cerebellar syndromes currently described. SCA3 is the most common SCA subtype worldwide, accounting for approximately 20% of SCA cases, followed by SCA2 (approximately 15%), SCA6 (approximately 15%), and SCA1 (approximately 5%). SCAs with greater extracerebellar pathology (eg, SCA1, SCA2, and SCA3) have more prominent cognitive deficits than those with purer cerebellar involvement (eg, SCA6). However, some features of cerebellar cognitive affective syndrome have been appreciated even in the isolated ataxic syndromes, including SCA6.[100] Executive dysfunction is the most commonly encountered cognitive phenotype in

CASE 4-2

A 59-year-old man was referred to the movement disorders clinic by his primary care doctor for balance difficulty over the past 2 years. He reported frequent stumbles and near falls, which happened more frequently on uneven surfaces, such as grass, or in dimly lit environments. He had some numbness and tingling in both feet. He had a tremor in both hands for about 10 years, right worse than left and most noticeable when using utensils or writing. The tremor was previously diagnosed as essential tremor; prior treatments with propranolol were ineffective, and primidone caused confusion and somnolence. He also noticed resting tremor for about the past year. Although he denied any changes in his cognition, his daughter, who accompanied him to the visit, was concerned that he was less active and engaged in his usual activities and more forgetful. He lived alone and seemed to be managing all of his daily tasks well. He had no family history of similar symptoms, although his daughter mentioned that she was starting fertility treatments in an attempt to start her own family.

On examination, his Montreal Cognitive Assessment (MoCA) score was 27/30, producing only five words on lexical fluency and a delayed recall of 3/5 words. Mild bradykinesia was present, as well as mild dysmetria on both finger-to-nose and heel-to-shin testing. He had an infrequent resting tremor of the right hand and a more prominent action tremor in his upper extremities bilaterally. Deep tendon reflexes were decreased throughout. His gait was wide based with normal stride length, foot clearance, and arm swing bilaterally but impaired tandem gait. A T2-weighted image from the patient's brain MRI is shown in FIGURE 4-1.

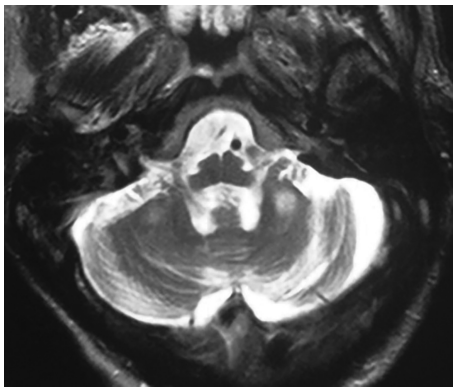

FIGURE 4-1
MCP sign on axial T2-weighted MRI, referring to hyperintensity in the middle cerebellar peduncles, most commonly seen in fragile X-associated tremor/ataxia syndrome (FXTAS).

the SCAs, although other features of the cerebellar cognitive affective syndrome can be seen. SCA1 can have more prominent executive dysfunction than SCA2 or SCA3, as well as verbal memory impairment.[101] The degree of cognitive impairment in SCA1 does not seem related to trinucleotide repeat length or even to disease duration.[102] Dementia is reported in 19% to 42% of patients with SCA2, with primarily executive and verbal memory deficits; no clear relationship has been established between repeat length and cognition.[103] Dementia is somewhat less common in SCA3, affecting 5% to 13% of patients.[104] Cognitive impairment is most frequently seen in SCA17, with more than 80% of patients being diagnosed with dementia during the course of their disease.[105] Dementia is more frequently

COMMENT

With a mix of movement phenomenologies, including an action and resting tremor, parkinsonism, and ataxia, as well as mild cognitive changes, this case presents a range of potential diagnostic possibilities. Without a clear family history, genetic ataxias would be less likely, although not impossible in the case of a sporadic mutation. However, the patient's daughter's infertility raises the possibility of premature ovarian failure, which can be seen in female carriers of an *FMR1* mutation. With a mixed tremor and ataxic features, evaluation for fragile X-associated tremor/ataxia syndrome (FXTAS) should be initiated with brain MRI and *FMR1* gene testing. Although T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the middle cerebellar peduncles (MCP sign) are characteristic of FXTAS, they are not necessarily specific, as these findings have been described in other neurodegenerative conditions affecting the pontocerebellar white matter, such as multiple system atrophy or spinocerebellar ataxias. An *FMR1* CGG repeat size between 55 and 200 is consistent with FXTAS.

present in cases of SCA17 with greater than 50 CAG or CAA repeats in *TBP*.[106] SCA17 should be considered in patients presenting with a behavioral variant frontotemporal dementia phenotype and a positive family history of neurologic conditions but negative genetic testing for frontotemporal dementia genes (*C9orf72*, *MAPT*, *GRN*), especially if cerebellar atrophy is present on neuroimaging. The most common age of onset is between 20 and 30 years for SCA17, but it can range from 3 to 75 years; age of onset has not been associated with repeat length. SCA17 is also one of the known genetic causes of psychiatric symptoms, with common features of depression, aggression, personality changes, poor self-care, and psychosis.[107]

Friedreich Ataxia

Friedreich ataxia is the most common hereditary ataxia, with a prevalence rate of 1 in 29,000.[108] Caused by an unstable GAA repeat expansion in the *FXN* gene, encoding the frataxin protein, Friedreich ataxia presents with a progressive cerebellar ataxia, limb spasticity, areflexia, scoliosis, sensory neuropathy, and cardiomyopathy. Although Friedreich ataxia typically presents between the ages of 10 and 15 years, 15% of cases present after the age of 25. Genetic testing for Friedreich ataxia should be considered in any patient with gait and/or limb ataxia, dysarthria, vibratory sensory loss, and/or abnormal eye movements, regardless of the age of onset. Cognitive impairment can be seen in Friedreich ataxia, especially with earlier ages of disease onset, more severe ataxia, and greater length of GAA repeat expansions.[109] Slowed cognitive processing speeds are detected, as well as impairments in executive function, attention, visuospatial function, and conceptual thinking.[110,111] Other cerebellar cognitive affective syndrome features, including impulsivity, irritability, and blunting of affect, can be seen in people with Friedreich ataxia.[112]

Niemann-Pick Disease Type C

Niemann-Pick disease type C is an autosomal recessive lysosomal storage disorder caused by *NPC1* or *NPC2* gene mutations that lead to abnormalities of intracellular sterol trafficking.[113] Niemann-Pick disease type C can present across the lifespan, although 50% of patients present before the age of 10 years. Characterized neuropathologically by AD-like neurofibrillary tangles, neuroaxonal dystrophy, and demyelination, Niemann-Pick disease type C causes variable degrees of cognitive impairment, as well as ataxia, dystonia, dysarthria, dysphagia, and vertical gaze palsy. Cataplexy and seizures can be seen in Niemann-Pick disease type C.[114] The adult-onset form presents as a chronic neurodegenerative condition, usually with psychiatric symptoms first, followed by ataxia, and then later cognitive decline. The psychiatric features of Niemann-Pick disease type C can mimic obsessive-compulsive disorder or bipolar disorder, and psychosis can occur.[115] Cognitively, impairments in executive and visuospatial functions are most frequently reported in Niemann-Pick disease type C; verbal memory is preserved.[116]

OTHER MOVEMENT DISORDERS WITH COGNITIVE FEATURES

Cognitive features are increasingly recognized in conditions previously considered "pure" movement disorders, including dystonia and essential tremor. In addition, medications commonly used for dystonia and essential tremor can have side effects of cognitive impairment, including anticholinergics (eg, trihexyphenidyl), antiseizure medications (eg, primidone, topiramate,

gabapentin), and benzodiazepines. Caution is advised in administration of these medications to patients of older age or with baseline cognitive changes.

Dystonia

Nonmotor symptoms, including cognitive and behavioral symptoms, are increasingly reported in dystonia.[117] Cognitive changes may vary based on the type and location of dystonia, with further research needed, and may be independent of motor symptom severity, level of disability, and mood symptoms.[118] Attentional and executive deficits have been described in primary dystonias, as well as impairments in social cognition. Deficits in facial expression recognition, especially for disgust[119,120] and in recognition of social faux pas, have been reported in people with cervical dystonia.[121]

Essential Tremor

With the appropriate removal of "benign" from its name, awareness of the nonmotor symptoms of essential tremor has been increasing. *Essential tremor-plus* is a suggested term from the reclassification of tremor, referring to cases of essential tremor with additional neurologic signs other than action tremor (eg, cognitive impairment, dystonia, rest tremor).[122] The utility and validity of this distinction remain unclear, however, especially as essential tremor is already a heterogeneous condition.[123] Although no consistent pattern of essential tremor–associated cognitive impairment has emerged yet, mild impairments have been detected in attention, working memory, executive function, verbal fluency, and visuospatial function.[124] Despite the mild degree of these impairments on formal cognitive testing, cognitive symptoms have been found to contribute to disease burden for those living with essential tremor.[124] Furthermore, the risk of dementia is increased in those who develop essential tremor later in life, especially after the age of 65 years.[125] This highlights not only the broader underlying pathophysiology of essential tremor and the essential tremor-plus syndromes but also the importance of regular screening for cognitive changes in older adults with essential tremor.

Pathologic studies of essential tremor reveal cerebellar abnormalities, including morphologic changes and loss of Purkinje cells, abnormal distribution of connections between Purkinje cells and climbing fibers, and reduced γ-aminobutyric acid (GABA) receptors in the dentate nucleus.[126] Essential tremor may be conceptualized as primary Purkinje cell dysfunction leading to reduced inhibitory output from the cerebellum to the cortex; these cerebellar abnormalities could therefore contribute to features of cerebellar cognitive affective syndrome. These neuropathologic changes are qualitatively similar to those in other conditions that cause primary cerebellar degeneration, such as SCA and MSA, although they are milder overall with some unique distinguishing features.[127] Although pathologic findings can distinguish essential tremor from other cerebellar disorders, no pathologic features differentiate essential tremor from essential tremor-plus cases.[128]

PRINCIPLES OF MANAGEMENT FOR COGNITIVE SYMPTOMS IN NON-PARKINSONIAN MOVEMENT DISORDERS

Few evidence-based, effective options are available for the treatment of cognitive impairment or dementia in nonparkinsonian movement disorders. Trials with cholinesterase inhibitors and/or memantine can be initiated on a case-by-case basis, recognizing limitations in effectiveness, safety profile, and

KEY POINTS

- Patients with fragile X-associated tremor/ataxia syndrome may present with action tremor, ataxia, or neuropathy.
- Screening for the *FMR1* premutation should be considered for patients with atypical parkinsonian syndromes and dementia.
- Family history is important in the evaluation of fragile X-associated tremor/ataxia syndrome, including clues of premature ovarian failure and intellectual disabilities.
- Cognitive changes are common in spinocerebellar ataxias, with spinocerebellar ataxia type 17 most frequently associated with dementia.
- If a patient presents with symptoms similar to those of a behavioral variant frontotemporal dementia with a positive family history of neurologic conditions but genetic testing for frontotemporal dementia genes (*C9orf72*, *MAPT*, *GRN*) is negative, spinocerebellar ataxia type 17 should be considered, especially if cerebellar atrophy is present on neuroimaging.
- Although Friedreich ataxia typically presents between the ages of 10 and 15 years, 15% of cases present after the age of 25.
- Consider genetic testing for GAA expansion in the Friedreich ataxia gene in any patient with gait and/or limb ataxia, dysarthria, vibratory sensory loss, and/or abnormal eye movements, regardless of the age of onset.

KEY POINTS

- **Patients with dystonia or essential tremor with cognitive symptoms should first be evaluated for medication-related effects.**
- **Essential tremor can cause neurologic symptoms beyond an action tremor, which could be termed *essential tremor-plus*; the distinction etiologically or pathologically between essential tremor and essential tremor-plus is not clear.**
- **Pathologic changes are present in the cerebellum in essential tremor, resulting in reduced inhibitory outflow from the cerebellum to the cortex.**

regulatory approvals. Clinicians should pay attention to other factors contributing to cognitive decline and encourage a brain-healthy lifestyle and modification of any existing risk factors. Large randomized placebo-controlled trials for cognitive-enhancing treatments in movement disorders are needed. Psychosocial support for patients and their care partners is also necessary, as are safety evaluations and monitoring.[129] The overlap of clinical manifestations seen within the movement disorders, including cognitive and behavioral symptoms, presents a ripe opportunity for multidisciplinary care models. Collaboration among neurologists, psychiatrists, psychologists, neuropsychologists, geneticists, rehabilitation specialists, and social workers could lead to improved care for these complicated clinical cases.

CONCLUSION

Neurodegenerative conditions, including those classified as movement disorders, rest firmly at the intersection between motor, cognitive, and behavioral clinical features; rarely does an isolated "pure" movement disorder exist. Awareness of this overlap and common presentations within the specific conditions can help improve accurate diagnosis and appropriate treatments. As cognitive symptoms directly correlate with impaired daily function and independence, worsened quality of life, and increased overall disease burden, additional research is needed to better understand their underlying causes and relevant pathophysiology and develop more effective treatments.

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