Management of Motor Symptoms in Dementia Disorders

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Zeynep Tufekcioglu, Basar Bilgic, Hasmet Hanagasi, and Murat Emre

List of Abbreviations

AD	Alzheimer's disease
bvFTD	Behavioural variant FTD
CBD	Corticobasal degeneration
CBS	Corticobasal syndrome
DLB	Dementia with Lewy Bodies
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTD	Frontotemporal dementia
HD	Huntington's disease
JHD	Juvenile Huntington's disease
MND	Motor neuron disease
MSA	Multisystem atrophy
PD	Parkinson's disease
PDD	PD dementia
PPA	Primary progressive aphasia
PSP	Progressive supranuclear palsy
svPPA	Semantic variant PPA
UPDRS	Unified Parkinson's Disease Rating Scale
VCI	Vascular cognitive impairment
VaD	Vascular dementia
VaP	Vascular parkinsonism

Z. Tufekcioglu (✉)
Faculty of Medicine, Department of Neurology, Istanbul Aydin University, Istanbul, Turkey

B. Bilgic · H. Hanagasi · M. Emre
Istanbul Faculty of Medicine, Department of Neurology, Movement Disorders and Behavioural Neurology Unit, Istanbul University, Istanbul, Turkey

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Introduction

Movement and cognition are the core functions of the nervous system, they are intricately integrated through large-scale networks. As a consequence, co-occurrence of motor and cognitive symptoms are common, encountered in many neurological diseases. Neurodegenerative disorders are slowly progressive entities, typically starting from a distinct area of the central nervous system and spreading to adjacent or inter-connected areas. Depending on the site of origin, motor symptoms can accompany cognitive impairment already at the onset of the disease or emerge as a result of progression of pathology in many neurodegenerative diseases.

Dementia disorders are among the leading causes of disability, especially in the elderly. One of the challenges in the management of dementia is the co-occurrence of cognitive impairment and motor symptoms (Table 10.1), which lead to increased disability and consequent institutionalization. Successful management of motor symptoms is critical to reduce disability and socioeconomic burden of dementias.

There are a variety of motor symptoms which may be seen during the course of the disease in different types of dementias (Table 10.2). These include both hypo- and hyper-kinetic symptoms such as parkinsonism, tremor, dystonia, chorea, myoclonus, and various gait disorders. In this chapter, we will review pharmacological

Table 10.1 Motor symptoms which may be associated with dementia

Motor symptom	Definition
Tremor	Oscillatory, typically rhythmic, and regular movement that affects one or more body parts
Bradykinesia	Slowness of movement unrelated to weakness or spasticity
Akinesia	Loss of movement unrelated to weakness or spasticity
Rigidity	Increased muscle tone to passive motion which is present equally in all directions of the movement
Postural instability	Difficulty righting himself or herself after being pulled off balance
Dystonia	Movements that tend to be sustained at the peak of the movement are usually twisting and frequently repetitive, and often progress to prolonged abnormal postures
Paratonia	Resistance to passive movement of the limb
Myoclonus	Sudden, brief, shock-like involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus)
Chorea	Involuntary, irregular, purposeless, non-rhythmic, abrupt, rapid, un-sustained movements
Ataxia	Decomposition of movement flow due to breakdown of normal coordinated execution of a voluntary movement
Hemiparesis	Weakness or inability to move one side of the body
Apraxia	a higher-order motor deficit in executing or planning motor acts that cannot be explained by weakness, spasticity, rigidity, akinesia or sensory loss.
Alien limb	Involuntary movements of an arm or leg which spontaneously moves to adopt odd postures beyond the control or understanding of the patient

Adapted from Fahn et al. [1]

Table 10.2 Dementia disorders associated with motor symptoms

Alzheimer's disease
Dementia with Lewy bodies
Parkinson's disease dementia
Vascular dementia
Normal pressure hydrocephalus
Frontotemporal dementia
Corticobasal degeneration
Progressive supranuclear palsy
Huntington disease
Multisystem atrophy

and non-pharmacological modalities used to treat such motor symptoms. In general, there is a lack of randomized controlled trials on the treatment of motor symptoms associated with dementia, in particular on non-pharmacological treatments.

Management of Motor Symptoms in Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of neurodegenerative disorders. The proto-typical form of AD begins with gradually progressive worsening of memory. As the disease progresses, other cognitive symptoms and non-cognitive features including behavioural, autonomic, and motor symptoms emerge. There are also other initial presentation forms of the disease defined as "atypical AD", including presentations by visual-spatial, aphasic, behavioural, or apraxic symptoms. Although very rare, AD may begin with motor symptoms such as cerebellar ataxia or hemiparesis. Corticobasal syndrome (CBS) may constitute another presentation form of AD presenting with an asymmetrical akinetic-rigid syndrome and limb apraxia; dystonia, myoclonus, and alien limb may be seen in the course of the disease [2, 3]. In contrast to more subtle and later emerging motor symptoms associated with the typical amnestic form, CBS due to AD pathology is associated with substantial motor symptoms, including limb apraxia (90%), myoclonus (81%), and gait disorders (70%) [3].

In the typical, amnestic form of AD, gait disorders, and other movement disorders emerge usually in the later stages of the disease. Motor symptoms in AD are significant and independent predictors of increased cost of care [4]. In a multi-centre study including 533 patients with AD at early stages, the presence of postural-gait impairment was associated with increased risk for institutionalization and mortality whereas the presence of tremor and bradykinesia was linked to increased risk for cognitive and functional decline [5].

There has been some confusion on defining the type of extrapyramidal symptoms seen in AD, in particular features of parkinsonism. Parkinsonian type rigidity has not been discriminated from paratonia in many studies. Unified Parkinson's Disease Rating Scale (UPDRS), which has been used in many studies, may not be ideal for distinguishing parkinsonism from signs that may be mistaken for it such as

"gegenhalten", and its use may lead to inaccurate results. The discrepancy in definitions and methodology gave rise to highly variable rates of parkinsonism seen in AD patients ranging from 20 to 100% [6]. On average parkinsonism develops in approximately 1/3 of AD patients and is associated with more severe functional impairment. Most common parkinsonian features are rigidity, bradykinesia, and postural instability, resting tremor is relatively rare. Progression of parkinsonian signs except for tremor is twice as rapid in AD compared to Parkinson's disease (PD) patients [7].

AD patients have an increased rate of falls ranging from 60 to 80%, twice as much as compared to their age-matched cognitively healthy peers. Risk factors for falls include severity of dementia, balance and gait problems, loss of vision, presence of depressive and autonomic symptoms, and use of medications including neuroleptics, hypnotics, and anxiolytics [8]. Falls may lead to serious medical consequences such as death, fractures, and hospitalization. Their aetiology should be evaluated carefully and necessary precautions should be taken.

Myoclonus is another movement disorder seen in AD patients. Its frequency increases gradually over time, younger-onset AD patients are more likely to develop myoclonus. In late-onset AD patients, myoclonus is a late feature; however, it may occur early in younger-onset patients, especially those carrying presenilin 1 (PSEN1) mutations. Along with a variety of drugs used for the symptomatic treatment of AD, both acetylcholine esterase inhibitors and memantine may induce myoclonic jerks in AD patients.

Paratonia, also named "gegenhalten", is a common motor phenomenon in late-stage AD patients. It is characterized by resistance to passive movement of the limb. Unlike rigidity, where there is a constant resistance to passive movement, the speed of movement increases the amount of resistance in paratonia. It is not specific for AD and may be seen in other types of dementia, the presence of paratonia has been associated with a more rapid decline [9]. Since the treatment strategies differ, it is important to differentiate paratonia from rigidity.

The neuropathological substrate of gait disorder and extrapyramidal symptoms in AD is not well established. In a pathological study, it was suggested that neuronal loss in substantia nigra due to tau pathology may be the underlying cause of extrapyramidal symptoms [10]. Another study revealed that alpha-synuclein aggregation and hyperphosphorylated tau accumulation in substantia nigra were associated with extrapyramidal signs observed in AD [11].

Pharmacological Treatment of Parkinsonism in AD

Although parkinsonism is a common feature in the course of the disease, there have been no randomized controlled clinical trials on pharmacological treatment of parkinsonism in AD. Levodopa may provide some benefits, although this needs to be confirmed and it has the potential to induce or worsen behavioural symptoms such as hallucinations. Dopamine agonists and anticholinergics carry a high risk to induce hallucinations and worsen cognitive functions, they should be avoided in AD patients. A small study with galantamine, an acetylcholinesterase inhibitor used in

the treatment of cognitive and behavioural symptoms of AD patients, suggested that it may also improve gait [12]. Donepezil was also reported to improve gait in early-stage AD patients in a small phase II trial [13]. Memantine, which is indicated for symptomatic treatment of AD, is an uncompetitive antagonist of *N*-methyl-D-aspartate receptor, also acts as a dopamine D2 receptor agonist. In a small study, improvement in stride time was observed in AD patients receiving memantine (20 mg/day) compared to patients receiving no treatment [14]. All these findings have been in small studies and need confirmation before these drugs can be considered for treatment of motor symptoms in AD.

Non-pharmacological Treatment of Parkinsonism in AD

There has been an increasing interest in the relationship between exercise and cognitive functions in AD. A systematic review, including six randomized clinical trials, showed a positive effect of exercise on the rate of cognitive decline in AD [15]. There are few studies on the effect of exercise and physical therapy on motor signs in AD. A systematic review revealed a moderate effect of exercise on both activities of daily living and physical function, including gait, balance, agility, and strength in AD patients [16]. Home-based exercise programs using computerized game councils have also been reported to show improvements in balance [17].

Treatment of Falls

The aetiology of falls in AD patients is heterogeneous, and treatment should target the underlying etiologic factors. In case falls are mainly related to parkinsonism, levodopa may be initiated empirically although evidence for its efficacy is lacking. In case autonomic dysfunction is the underlying factor, medications that may cause orthostatic hypotension such as antihypertensives, neuroleptics, anxiolytics, and drugs to treat prostate hypertrophy should be discontinued or their dose should be reduced. General principles to avoid orthostatic hypotension including increased intake of fluids and salt (provided there are no contraindications such as renal failure), sleeping with elevated head, abdominal compression and wearing anti-embolic stockings may be useful. In case these measures are not sufficient drugs such as midodrine, fludrocortisone, and pyridostigmine may be considered to increase standing blood pressure, but supine hypertension should be monitored.

Treatment of Myoclonus

Myoclonus in AD is thought to be of cortical origin. Hence, anti-myoclonus drugs known to be effective against cortical myoclonus are first-line treatments. These drugs, however, may be associated with significant adverse events, including cognitive worsening. Therefore, drug treatment should be considered only when

myoclonic jerks lead to severe disability or discomfort. Clonazepam, levetiracetam, and valproic acid are the most commonly used medications in AD patients; however, there are no controlled studies with these drugs in this population. Clonazepam should be initiated at low doses (0.5 mg) and gradually titrated up at 5–7 days intervals if needed; doses up to 3 mg/day may be required [18]. The most common side effect is drowsiness, patients may fall because of its sedative effect. Levetiracetam, an anti-epileptic drug, should also be initiated at low doses (500 mg/day) and can be titrated up to 3000 mg/day as necessary. Drowsiness and behavioural changes may occur and should be monitored. Valproic acid is another option, the initial dose should be 250 mg/day, doses around 1000 mg/day are usually needed for sufficient response. Drug-induced parkinsonism and tremor should be monitored in this particularly vulnerable population. It is contraindicated in patients with hepatic failure, and it has the potential to interact with warfarin.

Treatment of Paratonia in AD

No evidence-based treatment is available for managing paratonia in dementia patients. In a small study, botulinum toxin injections showed some beneficial effects, such as increasing the range of motion and reducing caregiver burden [19]. No data is available on the effect of benzodiazepines and baclofen, which are frequently used to treat spasticity and dystonia, other conditions associated with increased muscle tone. A 4-week randomized clinical study, including 101 dementia patients, assessed the effect of passive movement therapy for paratonia and found no benefit [20]. A small study reported that patients might benefit from supporting cushions [21].

Treatment of Motor Symptoms in Parkinson's Disease Dementia and Dementia with Lewy Bodies

In contrast to AD, motor symptoms are initial symptoms and always present in patients with PD dementia (PDD) and they occur in the vast majority of patients with Dementia with Lewy Bodies (DLB), either at the onset or during the course of the disease. There are substantial similarities in the pathological and clinical features of the two diseases, "one-year rule" has been proposed to differentiate these two conditions from each other: in case motor symptoms occur concomitantly with symptoms of dementia or ensue within 1 year of their onset the condition should be defined as DLB whereas it should be defined as PDD in case symptoms of dementia occur at least 1 year after the onset of motor symptoms.

In PDD patients, motor symptoms are generally more symmetrical with a predominance of bradykinesia, rigidity, and postural instability compared to non-demented PD patients. Tremor is less frequent or may disappear as dementia develops in those who initially had tremor [22]. Similar to PDD, an akinetic-rigid phenotype predominates also in patients with DLB, with bradykinesia, rigidity and

postural instability as core features. Tremor is less frequent, symptoms tend to be more symmetrical from the onset and during the course of the disease in contrast to the usual asymmetrical presentation of PD. Falls are frequent in both DLB and PDD, they may be the most disabling symptom in some patients leading to severe injuries and institutionalization, recurrent falls is also a supportive diagnostic feature for DLB. Major risk factors associated with falls in DLB and PDD patients are the severity of parkinsonism and dementia and the presence of autonomic symptoms, especially orthostatic hypotension. Medications administered to treat psychotic symptoms and REM sleep behaviour disorder such as neuroleptics and benzodiazepines may exacerbate orthostatic hypotension and can lead to falls. Approximately one-third of DLB patients develop myoclonus [23]. Myoclonus is usually located in the upper extremities and triggered by movement of the limbs or while maintaining a posture.

Pharmacological Treatment of Parkinsonism in DLB and PDD

Half of patients with DLB might show a clinical response to antiparkinsonian drugs [24]. Levodopa is the drug of choice, it should be started at low doses and slowly titrated to the effective and tolerated doses. Levodopa may induce or aggravate hallucinations and excessive daytime sleepiness which may be dose-limiting adverse effects and may render it difficult to attain effective doses. The magnitude of response to levodopa may differ across DLB patients. In a small study, Goldman et al. found a motor benefit (defined as >10% improvement over baseline in UPDRS Part III score) only in 1/3 of treated patients [25]. In another study including 24 DLB patients, positive response to levodopa challenge test was observed in approximately half of the patients. Initial response to levodopa was similar to that seen in PD patients; response to treatment, however, significantly decreased in the first year of treatment [26]. All together the results suggested that half of DLB patients may respond reasonably well to levodopa for a limited time period. The gradual loss of response to levodopa may be due to the predominance of axial symptoms in the later stages, which are usually non-levodopa responsive. The magnitude of motor response to levodopa also seems diminish with time in patients with PDD. In a study investigating response to levodopa in late-stage PD, Fabbri et al. included patients with advanced PD where 70% of patients had also dementia. They found a weak response to a supra-maximal dose of levodopa [27]. Dopamine agonists, monoamine oxidase inhibitors and in particular anticholinergics carry a high risk to induce or worsen behavioural and cognitive symptoms; they should be avoided in patients with PDD or DLB. A Phase II study of zonisamide, a drug approved for treatment of PD in Japan, showed benefits on motor symptoms of DLB patients when combined with levodopa [28].

There is no data on the management of dyskinesias in PDD and DLB. Amantadine, a drug commonly used to treat dyskinesias in PD patients, has the potential to induce or worsen hallucinations and should be used with caution. Clozapine, an atypical antipsychotic which also has some anti-dyskinetic properties, may be considered in

patients with both psychosis and severe dyskinesias. It may cause sedation and needs regular blood tests to monitor neutropenia and agranulocytosis which may be life-threatening.

Cholinesterase inhibitors are commonly used in the treatment of PDD and DLB. Donepezil is approved for treatment of DLB in Japan, whereas rivastigmine is world-wide registered for treatment of mild-to-moderate PDD. In a meta-analysis, both medications were found to have no significant effects on motor symptoms of DLB or PDD, rivastigmine may have a potential to worsen tremor in PDD patients [29].

Non-pharmacological Treatment of Parkinsonism in DLB and PDD

There is limited data on the effects of physical exercise in DLB patients. In a case report, stationary cycling (3 sessions/week for 8 weeks) resulted in an improvement of gait speed in a DLB patient [30]. In a small study, auditory rhythmical cueing was shown to improve gait in PD patients with cognitive impairment [31]. Evidence from studies conducted in PD patients suggests short- and long-term benefits of exercise. Hence, it seems reasonable to recommend exercise and physiotherapy to patients who have both dementia and parkinsonism including those with DLB and PDD.

Treatment of Falls in DLB and PDD

The aetiology of falls in this patient population is heterogeneous, it is important to reveal the underlying cause in any given patient with repeated falls. A classification of falls in PD was proposed as follows: (a) transitional (involves a basic transition from one posture to another, e.g., sitting on a sofa), (b) combined (involves everyday walking activities including stair climbing or combined movements, e.g., carrying heavy objects), (c) advanced (involves a complex, high-risk motor activity, e.g., hill walking) [32]. This classification is useful to identify the nature of falls in order to recommend appropriate strategies and exercises (e.g., strength or balance training in "transitional" type, neurocognitive strategies for "combined" type). It is important to recognize orthostatic hypotension as a cause of falls as opposed to those due to symptoms of parkinsonism since the treatment approaches differ. There is substantial data supporting the benefits of physiotherapy, exercise, and dance in reducing the risk of falls and increasing mobility in PD patients [33]. It is, however, not established if these beneficial effects persist in PD patients with dementia or those with DLB. Limited benefits of cognitive strategies such as dual-task, motor task, and complex motor task training to reduce risk of falling have been shown in cognitively healthy subjects and PD patients. However, none of these studies included DLB or PDD patients [34–37]. Although there is no evidence base, individualized exercise and physiotherapy programs fitted to the general,

physical and mental status of the patient can be recommended as good clinical practice.

Treatment of Myoclonus in DLB and PDD

Myoclonic jerks seen in patients with DLB are similar to those observed in AD, and strategies for their pharmacological treatment are similar. A caveat is the potential risk for worsening of parkinsonism with valproate in patients with DLB and PDD, treatment with levetiracetam or clonazepam should be preferred in this patient population.

Treatment of Motor Symptoms in Vascular Dementia

Vascular dementia (VaD) is a common form of dementia in which, vascular pathology of various origins is responsible for cognitive, motor, and autonomic symptoms. VaD is not a single disease, it spans a group of syndromes due to varying vascular mechanisms. As an umbrella term, vascular cognitive impairment (VCI) refers to the entire spectrum of cognitive disorders associated with vascular pathology.

In contrast to AD, motor symptoms are usually present in the early stages of VCI. As is the case for the definition of VCI, "vascular parkinsonism" is also a broad term that encompasses motor features of VCI, such as gait disorders, lower body predominant rigidity and bradykinesia, postural instability, freezing of gait, and pyramidal signs. Apart from usually symmetrical lower body parkinsonism, PSP-like syndrome or unilateral parkinsonism may rarely be seen in patients with VCI.

Recently, definition and classification of vascular parkinsonism (VaP) have been proposed by a panel of experts [38]. Acute or subacute presentation of parkinsonism due to vascular pathologies in brainstem or nigrostriatal pathways are defined as "acute/subacute post-stroke VaP" which is usually asymmetric and responsive to dopaminergic drugs. The "insidious onset VaP" is the most common subtype presenting with progressive parkinsonism together with pyramidal, cerebellar, pseudobulbar, cognitive, and urinary symptoms. Response to dopaminergic treatment in the insidious onset VaP subtype is usually poor. The "mixed type VaP" is defined as a clinical syndrome when cerebrovascular disease overlaps with neurodegenerative parkinsonism.

Neuroimaging is essential to demonstrate vascular changes to support the diagnosis of VaP. However, it should be kept in mind that concomitant vascular changes are frequent also in many neurodegenerative diseases, including Parkinson's disease. Severity of white-matter lesions in MRI was shown to be associated with higher UPDRS scores in VaP patients. In some instances, functional imaging with dopamine transporter ligands may help to differentiate VaP from PD by showing

normal dopaminergic activity in the basal ganglia of VaD patients provided that vascular lesions do not directly involve the striatum.

Neuropathology of VaP due to small-vessel disease involves perivascular pallor, gliosis, hyaline thickening, and widening of perivascular spaces in the subcortical white-matter, basal ganglia, and brainstem [39].

Pharmacological Treatment of Vascular Parkinsonism

The first step should be to identify and reduce the risk for further vascular damage in order to avoid progression of motor impairment; hence all vascular risk factors should be controlled as much as possible. Changes in lifestyle with pharmacological treatment of hypertension, diabetes mellitus, hyperlipidemia, and following the general guidelines for management of cerebrovascular disease have the potential to reduce the rate of progression of motor symptoms as well as dementia. Nevertheless, there have been no clinical trials that investigate effects of primary or secondary prevention strategies on the severity and progression of motor symptoms of VaD.

For symptomatic treatment, there is limited evidence to support the use of dopaminergic drugs. Levodopa has been reported to be the most beneficial dopaminergic agent in the treatment of motor symptoms of VaP. A study investigating the effect of levodopa in 17 pathologically confirmed vascular parkinsonism cases, a good response to levodopa was observed in 12 patients [39]. On contrary, many other studies showed limited response to levodopa in VaP patients. In a meta-analysis including 17 studies, rate of response to levodopa was 0.304 (95% CI of 0.230–0.388), indicating a low response rate [40]. In four of the studies included in the meta-analysis, UPDRS was used to measure the effect of levodopa on motor symptoms, the reduction in motor score ranged from 5.8 to 22.25% [41–44]. Two studies compared levodopa response in VaP versus PD patients and found a relatively low reduction in the UPDRS scores in VaP patients (5.9–18.7%) as opposed to substantial improvement in PD patients (31.6–64.65%) [42, 43]. There is evidence to suggest that VaP patients with nigrostriatal lesions are more likely to respond to levodopa compared to VaP patients without nigrostriatal lesions. In clinical practice, patients with vascular parkinsonism should receive levodopa in sufficiently high doses, and the treatment should be continued for a sufficient period of time to observe the response; higher doses as compared to those used in PD patients may be required. No data is available on the efficacy of dopamine agonists and monoamine oxidase inhibitors on the treatment of motor symptoms in VaP. An open-label study including 94 VaP and 92 PD patients suggested that vitamin D may have potential to decrease the rate of falls in patients with VaP by increasing muscle strength; no change in symptoms of parkinsonism was observed [45]. In a trial with 40 patients, drainage of cerebrospinal fluid was associated with improvement of gait in 15 patients with a mean duration of 2.4 ± 1.2 months [46]. In a small study, 5 Hz rTMS treatment was associated with a decrease in UPDRS motor scores [47]; a study with 25 Hz stimulation of supplementary motor cortex in VaP patients is in progress.

There are no controlled studies evaluating the effect of non-pharmacological approaches including rehabilitation or physiotherapy. Empirically, gait may benefit from conventional rehabilitation, and behavioural therapy may alleviate the fear of falling, these may be recommended as good clinical practice. Vascular dementia patients usually have primary motor symptoms such as hemiparesis, dysarthria or dysphagia which may benefit from stroke rehabilitation. Gastrostomy and enteral feeding should be considered in patients with severe dysphagia.

Management of Motor Symptoms in Frontotemporal Dementia

Frontotemporal dementia (FTD) is a syndrome characterized by progressive behavioural changes, executive dysfunction, and impairment in language functions, due to neuronal loss in frontal and temporal cortices and striatum, caused by various neurodegenerative disorders [48]. It is the leading cause of dementia before the age of 65 with an overall prevalence ranging from 3 to 26% [49]. Although the majority of cases are sporadic, a family history of dementia, motor neuron disease (MND) or parkinsonism are reported in up to 40% of cases; a clear autosomal dominant history accounts for 10% of cases [50]. Hexanucleotide (GGGGCC) expansions (>30 repeats) in the C9orf72 gene on chromosome 9, mutations in microtubule-associated protein tau, and progranulin genes are the most common (about 60% of all cases) genetic causes of familial FTD and may be associated with parkinsonism or MND [51, 52].

Based on the leading clinical features, three main subtypes have been defined including behavioural variant FTD, and two forms of primary progressive aphasia (PPA), i.e. semantic and non-fluent variants [53]. Behavioural variant FTD (bvFTD), the most common phenotype, manifests with progressive behavioural problems, inappropriate social conduct and executive dysfunction [54]. Semantic variant PPA (svPPA) is characterized by gradual loss of semantic knowledge impairing word comprehension. Non-fluent/agrammatic variant PPA presents with inability to plan and programme the motor aspects of speech and sentence construction [55].

A number of motor symptoms may accompany FTD, occurring usually in the later stages of the disease. These include hypokinetic movement disorders such as parkinsonism, impairment of eye movements, features of CBS as well as hyperkinetic movement disorders such as motor and vocal stereotypies, dystonia, chorea, orofacial dyskinesias, and myoclonus [56]. Although presynaptic dopaminergic dysfunction is involved in the development of parkinsonism, evidence suggests that postsynaptic dopaminergic dysfunction in the striatum may also play a role in the pathogenesis [57, 58].

MND or atypical parkinsonism may accompany both familial and sporadic forms of the disease [59–61]. Mild features of motor neuron disease can occur in up to 40% of FTD patients, 12.5% of patients with bvFTD develop MND with typical signs including upper and lower motor neuron symptoms, dysarthria, dysphagia, and pseudobulbar affect [62]. Epidemiological studies suggest that parkinsonism occurs in up to 50% of FTD patients, predominantly in bvFTD, rarely in svPPA, it

may also be associated with MND [54, 63–65]. Parkinsonism may be an initial feature of FTD, it can also emerge during the course of the disease [60, 61]. Atypical parkinsonism with symmetrical, axial akinetic-rigid syndrome, absence of tremor, and poor response to levodopa (including progressive supranuclear palsy phenotype) are the common features in several types of FTD, whereas asymmetrical parkinsonism and dystonia are the leading features in CBS phenotype [61, 66]. The most common hyperkinetic movement disorders in FTD are motor and vocal stereotypies, which have been observed in up to 78% of patients with autopsy-proven FTD. Chorea, orofacial dyskinesias, myoclonus, and dystonia are other hyperkinetic movements observed in some patients with FTD.

There are no randomized clinical trials on the efficacy of dopaminergic treatment for parkinsonism in FTD. Empirically a trial of levodopa up to 1000 mg/day can be given. Adverse effects such as nausea, hypotension, and psychosis may limit dose escalation. Typical neuroleptics should be avoided for the management of behavioural symptoms such as psychosis, quetiapine or clozapine may be considered with appropriate monitoring. Selective serotonin reuptake inhibitors may be considered for the management of stereotypies. In an open-label study fluvoxamine showed improvement in stereotypical behaviour in bvFTD and PPA patients [67]. Tetrabenazine (75 mg/day) has also been used in the management of stereotypies with some improvement [68]. Clonazepam may be used for the treatment of myoclonus [69]. Riluzole (100 mg/day) the only Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved treatment for MND [70] can be prescribed in FTD patients with motor neuron disease. Physical therapy with gait and balance training might be used to prevent falls and to decrease mortality [71]. Dysphagia is a common *symptom* of MND. Initial management approach should be modification of food and fluid consistency in patients with mild dysphagia. Liquids can be thickened and solid foods may be pureed, diced, or chopped. Gastrostomy and enteral tube feeding should be considered in more advanced patients to reduce the risk of aspiration pneumonia. There is, however, limited data to suggest that PEG placement is associated with prolonged survival [72].

Management of Motor Symptoms in Corticobasal Degeneration

Corticobasal Degeneration (CBD) is a neurodegenerative disease associated with abnormal aggregates of 4-repeat tau (4R-tau) protein. It is characterized by generally asymmetric movement disorders (levodopa non-responsive parkinsonism, dystonia, abnormal gait, and myoclonus) combined with partly lateralized symptoms of higher cortical dysfunction such as apraxia, alien limb phenomenon, cortical sensory loss, cognitive impairment, behavioural changes, and aphasia [73, 74].

Pathology confirmed studies have revealed that diverse clinical presentations are associated with CBD [73]. Conversely, different pathologies such as AD, FTD, progressive supranuclear palsy (PSP), DLB, and Creutzfeldt- Jakob disease might lead

to clinical features of classical CBD which is termed as corticobasal syndrome (CBS) [75]. It is estimated that 50% of CBS cases have CBD pathology [76].

There is currently no medication approved for the treatment of CBD. Drugs used for treatment are based on experience in other disorders or on non-randomized historical controls, case series, or expert opinions.

Clinicopathological series revealed that limb rigidity and bradykinesia were the most common motor findings in CBD [73]. Although levodopa response in parkinsonism is considered to be insufficient and excellent/sustained response is an exclusion criterium, it should be tried especially for bradykinesia and rigidity. Where present, benefits are often mild to moderate and transient [73]. Kompoliti et al. reviewed 147 CBS patients (7 were autopsy proven) and found clinical improvement with dopaminergic drugs in 24% of cases, 71% had no improvement [77]. Levodopa was introduced in 87% of all cases and 26% demonstrated modest response (median daily dosage 300 mg, range 100–2000 mg). Bradykinesia and rigidity were the best improved symptoms with levodopa. Dopamine agonists, selegiline, and amantadine were tried in limited number of cases (6–13%) and the response was worse than levodopa. Five percent of the patients experienced drug-associated worsening of parkinsonian features, dystonia, myoclonus, or gait dysfunction. Anticholinergics and benzodiazepines have been tried and found to be usually ineffective. Dyskinesias did not occur with dopaminergic drugs in this series, there are, however, few pathologically confirmed CBD cases who developed levodopa induced dyskinesias [78, 79].

Although dystonia was reported in up to 83% in clinical series and considered as one of the classical features of CBS, pathologically confirmed studies revealed that it was present only in 38% of CBD cases [80]. In the majority of cases presented with a corticobasal syndrome, dystonia occurred earlier (in the first 2 years from disease onset), mostly affecting the upper limb. In other phenotypes with cognitive presentations, dystonia tended to appear later and to affect the cervical region and face [80]. In the PSP phenotype blepharospasm and axial dystonia were the most frequent presentations. Generalized dystonia or hemidystonia may occur during the course of the disease [81, 82]. Dopaminergic agents, amantadine, anticholinergics, benzodiazepines, muscle relaxants (e.g., baclofen), and intramuscular botulinum toxin injections have been tried for the management of dystonia in CBD. Except for botulinum toxin injections, these medications were rarely effective [77, 80, 83]. Botulinum toxin can be useful for pain and hygiene problems due to contractures associated with dystonia. Deep brain stimulation is not recommended for patients with CBD [84].

Myoclonus is one of the common symptoms of CBD. The frequency in pathological series is 27–52% [73, 80]. Myoclonus is usually focal and considered to be of cortical origin. It can present as cortical reflex myoclonus, stimulus-sensitive myoclonus or action myoclonus. It is usually localized in the upper extremities, but can also be present in the face [79, 85, 86]. Low-amplitude action myoclonus may resemble tremor. A clinicopathological study revealed that myoclonus is more common in CBD-mimics [87]. Benzodiazepines (particularly clonazepam),

antiepileptics (levetiracetam, gabapentin, valproic acid), piracetam, and neuroleptics have been tried with variable results [77].

The role of exercise in CBD is not well studied. Nevertheless, regular exercise and appropriate physiotherapy may be recommended as good clinical practice in CBD patients with parkinsonism or gait problems [88, 89].

Management of Motor Symptoms in Progressive Supranuclear Palsy

PSP is a tauopathy characterized by parkinsonism, vertical gaze palsy, early postural instability with falls, dysarthria, dysphagia, and a dysexecutive type dementia [90, 91]. The phenotype of parkinsonism is usually a symmetrical, akinetic-rigid form with prominent postural imbalance; tremor is rare. Unprovoked falls are the most significant problem and the main cause of disability, prominent dysphagia, and dysarthria develop in almost all patients.

For treatment of parkinsonism, levodopa is the first drug of choice. While excellent or sustained response to levodopa has previously been a mandatory exclusion criterion, a subtype of PSP defined as PSP-Parkinson has been recognized, such patients may have clear benefit from levodopa, substantially more so as compared to other phenotypes of PSP [92], hence a clear response to levodopa is no longer an exclusion criterion for PSP. Although the evidence base for benefits of levodopa treatment is weak, due to lack of better options up to 1500 mg daily doses are commonly administered [83, 93–96]. There are a few uncontrolled studies which assessed the efficacy of dopamine agonists and which found no or limited benefits [83, 93, 94, 95, 97]. Monoamine oxidase B inhibitors have also failed to show any beneficial effect [83, 93, 95]. The *N*-methyl-D-aspartate-antagonist amantadine up to 600 mg/day has been reported to be of variable benefit in retrospective series [83, 95]. Botulinum toxin injections can be used for focal dystonias including apraxia of eyelid opening with variable success [96]. A study which assessed effects of deep brain stimulation in the pedunculopontine nucleus in eight PSP-RS patients did not show any benefits, there was no difference between on-stimulation and off- stimulation at 6 and 12-month follow-up [98].

Drugs used for the treatment of motor symptoms may lead to various adverse effects. Cognitive and behavioural symptoms may be exacerbated by medication used to treat movement disorders and other symptoms of PSP. Levodopa can cause orthostatic hypotension, hallucinations, delusions, gastrointestinal complaints, and dizziness, amantadine can lead to insomnia, confusion, hallucinations, postural hypotension, anxiety, anorexia, and livedo reticularis [99].

The effect of physiotherapy on motor symptoms has been investigated in a few studies. A randomized controlled study showed that physical exercise may improve balance and gait and reduce falls, the magnitude and duration of effects were, however, limited [100]. Effects of structured physical exercises in patients with advanced PSP are not known. In a systematic review, weight-supported treadmill training, music-cued movement rehabilitation, and robotic-assisted gait training were

reported to be beneficial in early PSP [101]. Eyeglasses with bifocal or prismatic lenses may help to look downwards without moving eyes in patients with downward gaze palsy [102]. As pharmacological treatments are of limited benefit in most patients, supportive measures including gait and balance exercises as well as measures to improve dysphagia are important.

Management of Motor Symptoms in Huntington's Disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded cytosine-adenine-guanine trinucleotide repeat in the huntingtin gene on chromosome 4 which encodes the huntingtin protein. Although medium spiny neurons of the striatum are particularly vulnerable to mutant huntingtin induced pathology, the disease affects the whole brain and body [103]. Clinically, Huntington's disease is characterized by motor symptoms, cognitive impairment, and psychiatric disturbances [103, 104]. Manifest HD is diagnosed in genetically confirmed or at-risk individuals with "unequivocal presence of an otherwise unexplained extrapyramidal movement disorder such as chorea, bradykinesia or rigidity" that indicates 99% diagnostic confidence for HD [105, 106]. Slow saccades and cognitive dysfunction are usually supportive findings for HD [103].

Two main components of motor disorder in HD are involuntary movements (chorea) and impaired voluntary movements (bradykinesia and incoordination). While chorea is common in adult-onset cases, bradykinesia is more common in juvenile onset patients in earlier phases of the disease [107, 108]. Bradykinesia, dystonia, and parkinsonism are more prominent features in Juvenile HD (JHD), and chorea may not be seen during the whole course of the disease. Myoclonus and epileptic seizures are also reported in half of the JHD patients. In adult-onset HD, chorea often decreases during the course of the disease whereas bradykinesia, dystonia, and rigidity begin to predominate and predict functional disability [103, 109, 110]. Dysarthria and dysphagia usually appear at the later stages of the disease.

Chorea is thought to be a result of imbalance between glutamate and dopamine activity in basal ganglia. Treatment for chorea is based on dopamine depletion or dopamine receptor blockade [111, 112]. Tetrabenazine, a synaptic vesicular amine transporter inhibitor 2 (VMAT2) depletes dopamine and has been licensed by the US FDA for the treatment of chorea in HD. The initial dose is 12.5 mg/day, titration should be done slowly by weekly intervals of 12.5 mg/day to identify dose that reduces chorea and is tolerated, maximum dose is 100 mg/day. The main and dose-limiting adverse events have been reported to be sedation, akathisia, parkinsonism, depression, and suicide attempt [113]. However, recent studies reported that use of Tetrabenazine is not associated with increased risk of suicide [114, 115]. Deutetrabenazine, recently approved by FDA, is a novel Vesicular Amine Transporter Inhibitor 2 inhibitor with prolonged active metabolite half-lives and has a favourable tolerability profile with lower adverse effect rates than tetrabenazine [116, 117]. The most common adverse events with deutetrabenazine include somnolence,

insomnia, headache, diarrhoea, and akathisia which are usually mild to moderate [118].

Chorea is also treated with typical or atypical neuroleptics (dopamine receptor blockers). These are, however, associated with potentially serious adverse effects such as parkinsonism, imbalance, akathisia, neuroleptic malignant syndrome, acute dystonic reactions, tardive dyskinesia, blunting of affect, and generalized apathy. Since parkinsonism dominates in the later stages of the adult-onset disease, use of neuroleptics requires caution. Neuroleptic drugs may be preferred in the treatment of chorea when accompanied with psychiatric symptoms. Tiapride (in Europe), olanzapine, and risperidone are preferred as the first-line treatment of chorea, in addition to Vesicular Amine Transporter Inhibitor 2 inhibitors [119]. Considering the glutamate arm of chorea pathophysiology, inhibitors of glutamate transmission (riluzole 200 mg/day, amantadine 400 mg/day) have also been tried. Although they are recommended in the 2011 AAN evidence-based guidelines, their use is controversial [120, 121].

Dopaminergic drugs, such as levodopa and dopamine agonists can be used to treat rigidity and bradykinesia [122]. They may be used in selected cases of JHD or in the late stages of the adult-onset disease, where hypokinetic symptoms are more prominent. They should be avoided in early stages of adult forms or late stages of JHD where chorea is more prominent. Based on limited data, non-invasive stimulation with transcranial magnetic stimulation to supplementary motor and primary motor area may be effective for chorea, depression, and cognitive functions; these effects, however, need to be confirmed in larger studies [123–125]. Deep brain stimulation of pallidum may be effective in the treatment of medically resistant chorea. It does not, however, seem to improve daily living activities, current data are limited, there are challenges such as severe pallidal atrophy, clinical variety in different stages of the disease and coexisting problems [125]. Baclofen, benzodiazepines, and botulinum toxin injections can be used to treat dystonia.

Physiotherapy should be part of the management of motor symptoms, recommendations have been published to guide physical therapy [126]. Aerobic exercise, resistance training, and supervised gait training are recommended to improve fitness, motor function, and gait with grade A evidence. It has been suggested that these approaches also improve balance although they do not reduce the frequency of falls. Inspiratory and expiratory training may be beneficial to improve respiratory functions. Educating caregivers on the value of these exercises may lead to a higher rate of engagement in training and integrating these into daily life.

Treatment of Motor Symptoms in Multisystem Atrophy

Multisystem atrophy (MSA) is a neurodegenerative disease associated with abnormal aggregates of fibrillary α-synuclein protein in both glia and neurons [127, 128]. Depending on the predominant clinical features, the disease is sub-classified as MSA-parkinsonism and MSA-cerebellar. Dementia was considered as a non-supporting feature of MSA clinical criteria, however, emerging evidence demonstrated

that approximately 30% of patients with MSA develop mild cognitive impairment. Cognitive decline sufficient to justify a diagnosis of dementia may be found in some patients with advanced stages of MSA [129, 130].

Response of parkinsonism to levodopa is variable and limited. In pathologically confirmed series, 30–70% of patients with MSA had an initial good response to levodopa [131–135]. In order to fully evaluate therapeutic response patients should be given up to a maximum dose of 1.5 g per day for at least 3 months [136]. One should be cautioned that levodopa may induce psychotic symptoms and worsening of orthostatic hypotension in the absence of any motor benefit. In a minority of patients with levodopa responsiveness, dyskinesia can develop, mostly at the craniocervical region and even after short-term use [137]. There are no controlled studies on the efficacy of dopamine agonists in MSA, in a retrospective study only 10% of patients had benefit with dopamine agonists [133]. Dopamine agonists also have a higher rate of side effects, especially worsening of orthostatic hypotension [138, 139], they are not recommended as first-line treatment. A retrospective case study revealed good response to amantadine in 15% of patients. A small, placebo-controlled study, however, failed to demonstrate any efficacy of amantadine in patients with MSA [140]. There is no evidence supporting the benefits of entacapone and Monoamine oxidase inhibitors in MSA [141, 142]. Because of limited experience suggesting poor outcome, and the possibility of harmful effects, DBS is not recommended in patients with MSA [143–145].

Although there are no randomized controlled studies, available data suggests that medical rehabilitation may improve balance, motor impairment, functional capacity, and reduce falls [146, 147].

Case Presentation

A 74-year-old female was referred to Memory Clinic for gradually progressive forgetfulness during the past 3 years with a rapid worsening in the last 3 months. Her memory problems included repeating questions, inability to recall new events, and recent conversations. She had trouble finding her way in familiar environments which had developed over the last 1 year, she became more apathetic and had increasingly more difficulty understanding complex sentences. Her movements became slower and resting tremor emerged on the right hand in the past few years. Her cognitive and motor performance fluctuated within the day as well as from today. Her past medical history was conspicuous for paranoid delusions for more than 30 years without hallucinations. There was no history of REM sleep behaviour or autonomic dysfunction. On admission she was receiving rivastigmine patch 4.6 mg/day, pimozide 4 mg/day for delusions, and trihexyphenidyl 4 mg/day as prophylaxis against extrapyramidal side effects. Her neurological examination revealed a right-sided resting tremor, mild-to-moderate rigidity, and bradykinesia, her gait was slow with short stride length and stooped posture. Mini mental state examination score was 19/30, her neuropsychological exam revealed deficits in memory (both encoding and retrieval), attention, executive, and visuo-spatial

functions. Cranial MRI revealed mild bilateral hippocampal and parietal atrophy. Differential diagnosis included Dementia with Lewy Bodies versus Alzheimer disease with secondary parkinsonism due to pimozide and aggravated cognitive impairment due to adverse effects of anticholinergic medication. Pimozide and trihexyphenidyl were discontinued, rivastigmine patch was increased to 9.6 mg/day. Her motor and cognitive symptoms improved within a month, mini-mental state examination score increased to 24/30, both gait and bradykinesia improved, but a slight resting tremor on the right hand as well as mild bradykinesia-rigidity remained. A treatment with L-dopa 300 mg/day was initiated upon which her tremor and bradykinesia further improved. Our final diagnosis was Alzheimer disease with concomitant Lewy-body pathology as well as drug-induced worsening of motor and cognitive symptoms.

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