Chapter 11
Atypical Parkinsonism

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Clinical Pearls

- Slowing of vertical saccades or restricted downward gaze can differentiate PSP from other parkinsonian disorders
- Postural instability and falls are not commonly an early feature in Parkinson's disease but are prominent in PSP
- Midbrain atrophy on mid-sagittal MRI gives the characteristic "Hummingbird sign", which may help differentiate PSP from other forms of parkinsonism
- Unilateral "hand clumsiness" is the most common presenting motor symptom in CBD.
- Markedly asymmetric upper limb apraxia, rigidity, and dystonia help differentiate CBD from other forms of parkinsonism
- Early and pronounced autonomic dysfunction differentiate both forms of MSA from all other forms of parkinsonism and most adult onset cerebellar ataxias
- Lack of resting tremor, cerebellar ataxia, rapid progression, poor response to levodopa, and MRI abnormalities are useful in differentiating MSA from PD
- MSA patients need comprehensive care involving multiple medical disciplines (urology, cardiology, sleep medicine, gastroenterology)

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Atypical Parkinsonism

Introduction

Parkinsonism refers to a variety of syndromes unified clinically by the presence of bradykinesia—a disorder of motor function resulting in slow, small amplitude movements [1]. The most common form of parkinsonism is Parkinson's disease (PD), while other forms are considered "atypical parkinsonism", and are divided into sporadic, familial, and secondary etiologies [2]. The sporadic forms of atypical parkinsonism consist of Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA), and Dementia with Lewy Bodies [2, 3]. This chapter will focus on the diagnostic criteria and care paths for PSP, CBD, and MSA. DLB is discussed in a separate chapter. Figure 11.1 shows a summary approach to atypical parkinsonism.

Progressive Supranuclear Palsy (PSP)

Introduction

Progressive Supranuclear Palsy (PSP) is a sporadic atypical parkinsonian disorder which manifests as progressive bradykinesia and rigidity, ocular motility disturbances, and early falls [4]. Although rare in the general population, it is the most common atypical parkinsonian disorder—approximately 6% of all parkinsonian patients evaluated at a specialty clinic are diagnosed with PSP [2].

Since the initial recognition of the classic PSP syndrome (also called "Richardson syndrome" or "PSP-RS"), several clinical variants have been identified and are commonly referred to as "Atypical PSP" [5]. This sub-classification is based on the initial predominance of symptoms and includes speech/language disorders (PSP-SL) including progressive apraxia of speech (PSP-AOS) and nonfluent/agrammatic primary progressive aphasia (PSP-nfaPPA), cerebellar ataxia (PSP-C), corticobasal syndrome (PSP-CBS), frontal lobe cognitive of behavioral presentations (PSP-F) including behavioral variant frontotemporal dementia (bvFTD), ocular motor dysfunction (PSP-OM), parkinsonism resembling idiopathic Parkinson's disease (PSP-P), postural instability (PSP-PI), primary lateral sclerosis (PSP-PLS), and progressive gait freezing (PSP-PGF). The unifying pathology of these disorders includes intracellular neurofibrillary tangle collection; the pathologic distribution and clinical severity differs with each subtype.

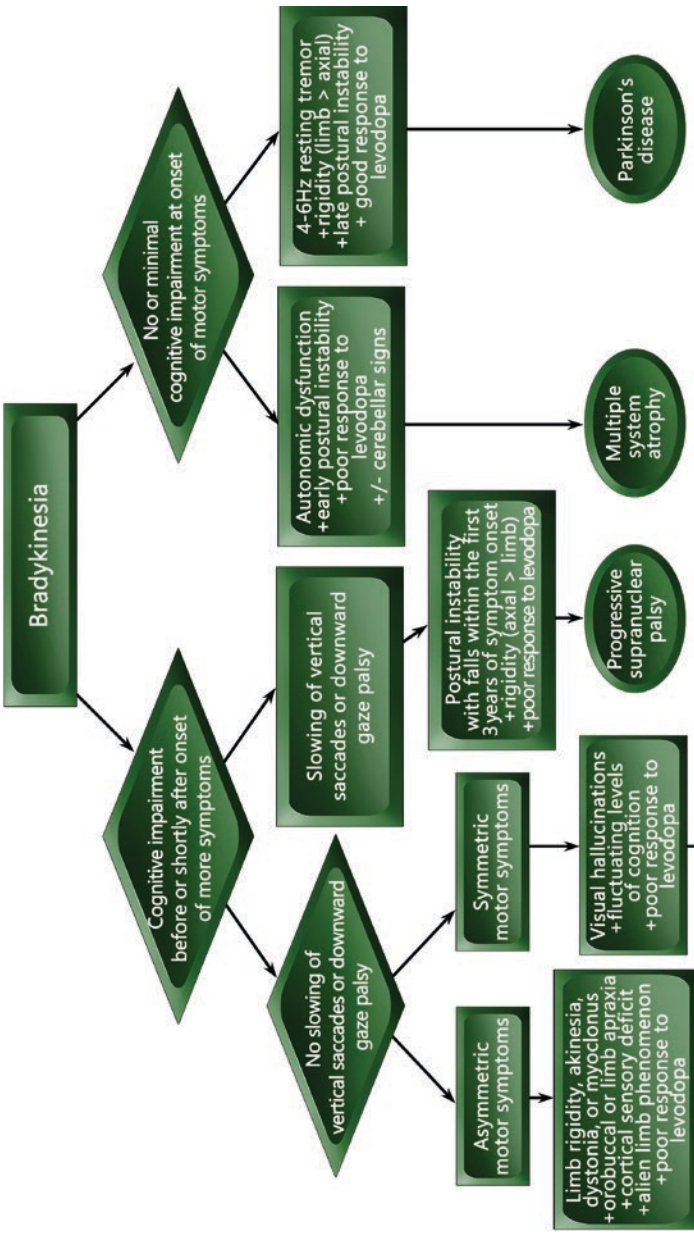

Fig. 11.1 Differential diagnosis of atypical parkinsonism

Clinical Manifestations

History

The average age of onset for PSP is 63 years old, a few years later than the average age of onset for Parkinson's disease [6]. The disease is rarely, if ever, seen in patients before age 40 and its diagnosis should be called into question in this age range [7]. The hallmarks of PSP are early postural instability with falls within the first year of disease onset, and vertical supranuclear gaze palsy [8].

Patients may initially experience personality changes, difficulty with balance, or vision disturbance. Bilateral bradykinesia is a common presenting symptom, seen in up to 88% of PSP patients presenting for the first time [8]. Most eventually pursue medical care after the onset of falls.

PSP patients experience their first fall a median of 16.8 months after onset of symptoms, falls after symptom onset take approximately 30 months in CBD, 40.8 months in vascular parkinsonism, 42 months in MSA, 54 months in DLB, and 108 months in PD [9]. Signs and symptoms shown to be associated with earliest falls (<2 years from symptom onset) include early cognitive dysfunction, symmetrical disease onset, axial rigidity, dysphagia, and eye movement abnormalities. Frontal lobe dysfunction manifesting as impulsivity and lack of insight further increases the risk of falls. Unexplained falls backwards, not associated with a loss of consciousness, are the most common clinical presentation of PSP.

Dystonia most commonly presents as blepharospasm, but may present as asymmetric limb or hemi-dystonia, or as axial dystonia [10]. Cervical dystonia is a common feature later in the disease, and can manifest as retrocollis, anterocollis, or torticollis [11]. Dystonia may be present as part of the natural course of the disease, or develop in response to levodopa administration. Dopaminergic medications may briefly improve the motor symptoms in the early stages of PSP, but more commonly there is little to no effect, and it may worsen gait abnormalities and balance [11].

Most patients eventually lose the ability to read or maintain persistent eye contact, and approximately 1/3 initially describe having blurred vision, eye discomfort, or double vision [10]. Patients rarely present with blatant complaints of being unable to look up or down. Eyelid dysfunction (ranging from a decreased blink rate to involuntary eyelid closure (blepharospasm), or failure to open upon command (eyelid freezing or apraxia of eyelid opening)) and difficulties with horizontal eye movements are markers of advanced stages of disease [12].

Early cognitive dysfunction is common in PSP, and may be the presenting symptom in up to 10% of patients [13]. Cognitive dysfunction seen in PSP usually manifests with impaired abstract thought, executive dysfunction, decreased verbal fluency, behavioral disturbances, and motor perseveration [14].

The disease progression in PSP is more severe and rapid than that seen in PD, with median survival ranging from 5 to 8 years [2]. With time, verbal fluency declines, axial rigidity and progressive immobility result, complete ophthalmoplegia may occur, and dysphagia worsens. Subsequently, death is most commonly secondary to respiratory complications, such as aspiration pneumonia or pulmonary emboli [15].

Physical Examination

The standard neurologic examination, with a focus on oculomotor evaluation, should be performed. Saccades, rapid eye movements to move the line of sight directly on the fovea, are evaluated by eliciting optokinetic nystagmus (OKN). This is commonly performed using a strip containing squares of alternating colors, asking the patient to look straight ahead while monitoring saccadic eye movements. Slowing of vertical ocular saccades (downbeat and upbeat) present early in the course of the disease, while horizontal saccades are affected later [16]. Vertical gaze paralysis occurs as the disease progresses, and may initially be overcome by the oculocephalic maneuver [11]. Patients may present with the "procerus sign": a wide-eyed look of astonishment or worry due to a combination of oculomotor abnormalities and rigidity, bradykinesia, and hypertonicity of the facial muscles [17].

The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and/or the Progressive Supranuclear Palsy Rating Scale (PSPRS) are commonly administered. Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetition [1]. Axial rigidity (clinically assessed by passive neck movement) is more pronounced than limb rigidity (tested by passive movement of the wrists, elbows, knees, and ankles). Patients are assessed for tremor at rest, with arms outstretched (postural tremor), and with movement (kinetic tremor). Tremor is a rare clinical feature of PSP-RS, but may be seen in PSP-P [1]. The classic gait seen in PSP is characterized by a stiff, broad-based posture, knee and trunk extension, and bilateral upper extremity abduction. Instead of the "en-bloc" turns seen in PD patients, PSP patients often pivot when they turn, which further increases the risk of falls [2]. Postural instability, an early and severe component of PSP, is assessed by the "pull test" (patients stand with feet apart and are pulled backwards at the shoulders by the examiner).

Cognition is typically assessed via the Montreal Cognitive Assessment (MOCA) or Mini Mental Status Examination (MMSE). Cognitive and behavioral changes are common in PSP, with deficits seen in numerous domains. Executive dysfunction is prominent, but memory and visuospatial deficits also occur. Apathy is frequently seen in PSP and patients may present concomitantly with impulsivity [18]. The severe episodic memory deficit observed in Alzheimer's disease is not typically present in PSP, and recognition usually is largely preserved [13].

Diagnostic Approach for PSP

The clinical diagnosis of PSP is based primarily on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. Figure 11.2 *provides a diagnostic algorithm for parkinsonism.*

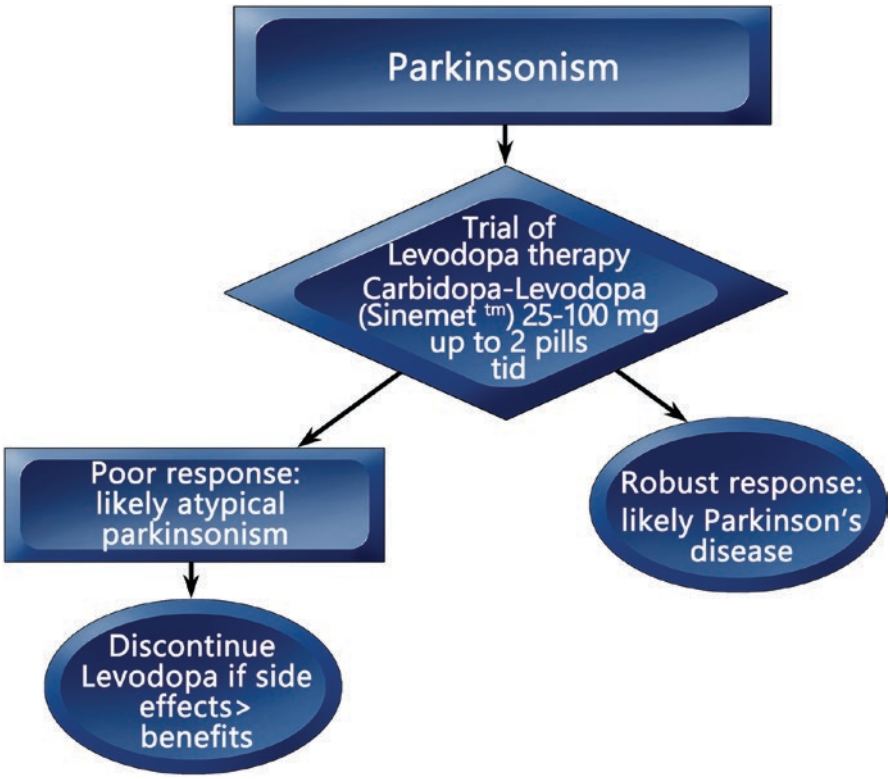

Fig. 11.2 Diagnostic algorithm for parkinsonism

Key history, examination, laboratory, and imaging criteria include:

History

- Prominent postural instability and falls within the first year of onset of symptoms
- Progressive onset of Parkinsonism (bilateral and symmetric bradykinesia, stiffness/rigidity, absence of tremor (unless PSP-P), worsening gait)
- May complain of blurred vision or difficulty reading (rarely complain of difficulty looking up or down)
- Early cognitive and behavioral abnormalities
- Rapid onset and progression of symptoms
- Limited or no response from levodopa

Neurologic Exam

- Slowing of vertical saccades or vertical supranuclear gaze palsy
- Prominent postural instability on pull test
- Bilateral and symmetric bradykinesia
- Axial > Limb rigidity
- Executive dysfunction, memory and visuospatial deficits on cognitive testing
- Table 11.1 shows the core clinical features of PSP

Imaging

MRI Brain

- (Fig. 11.3) Mid-sagittal MRI showing atrophy of the rostral midbrain tegmentum, caudal midbrain tegmentum, base of the pons, and cerebellum giving the appearance of the bill, head, body, and wing (respectively) of a hummingbird ("Hummingbird sign") [19]
- A study using the A-P diameter of the midbrain and pons on mid-sagittal MRI, showed a midbrain measurement of <9.35 mm had 83% sensitivity and 100% specificity for PSP [20].
  - A midbrain to pontine ratio of <0.52 had 67% sensitivity and 100% specificity for PSP compared to MSA [20].
- Cortical atrophy with a frontal predominance is generally present as well

Table 11.1 Core clinical features of PSP

Levels of certainty	Ocular motor dysfunction	Postural instability	Akinesia	Cognitive dysfunction
Level 1	01: Vertical supranuclear palsy	P1: Repeated unprovoked falls within 3 years	A1: Progressive gait freezing within 3 years	C1: Speech/language disorder, i.e., nonfluent/agrammatic variant of primary progressive aphasia or progressive apraxia of speech
Level 2	02: Slow velocity of vertical saccades	P2: Tendency to fall on the pull-test within 3 years	A2: Parkinsonism, akinetic-rigid, predominantly axial, and levodopa resistant	C2: Frontal cognitive/behavioral presentation
Level 3	03: Frequent macro square wave jerks or "eyelid opening apraxia"	P3: More than two steps backward on the pull-test within 3 years	A3: Parkinsonism, with tremor and/or asymmetric and/or levodopa responsive	C3: Corticobasal syndrome

Levels with lower numbers are considered to contribute higher certainty to a diagnosis of PSP than levels with higher numbers. (From Hoglinger et al. 2017 [5])

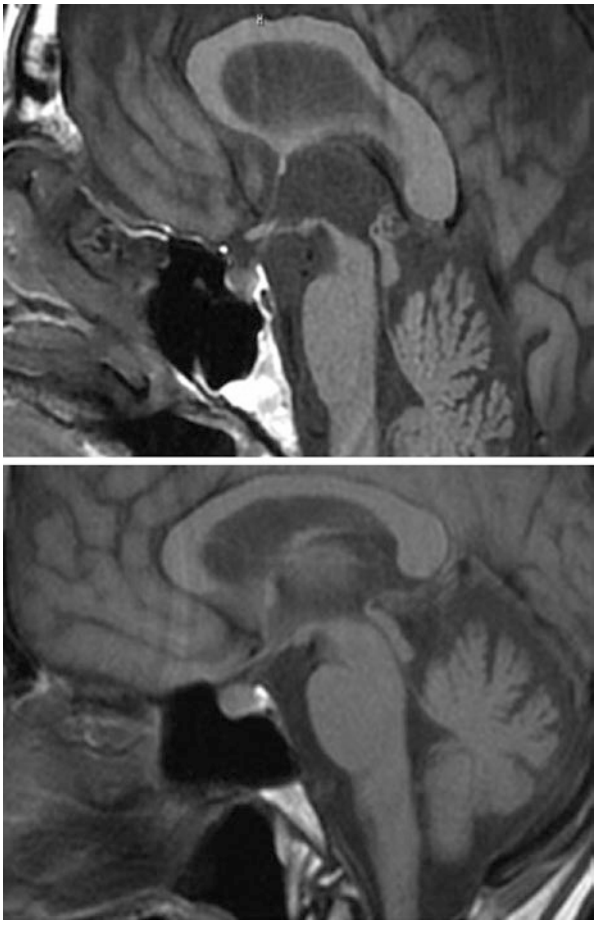

Fig. 11.3 The "Hummingbird sign" in PSP (midbrain atrophy characteristic of PSP [*top*], a normal control is shown [*below*] for comparison)

DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

Laboratory Testing

- Blood tests are typically of limited utility in diagnosing PSP
- CSF biomarkers are promising but need further validation

Genetic Testing

- Although considered a sporadic disorder, recent findings suggest there are likely predisposing genetic factors which are triggered in response to environmental factors such as oxidative stress [22].
- Currently, there are no genetic tests readily available to support or confirm a diagnosis of PSP.

Pathology

- Diagnosis of definite PSP can only be made by pathologic analysis upon autopsy
- Pathologically, PSP is characterized by aggregated tau protein forming neurofibrillary tangles in predominantly subcortical neurons, tufted astrocytes, and oligodendroglial inclusions [23]

Table 11.2 presents the diagnostic criteria for PSP.

Case Example

Example using the 2017 Movement Disorder Society Criteria for the Clinical Diagnosis of PSP:
A 64 year old gentleman presents to your office for evaluation of frequent falls. His first fall occurred two years ago - he was playing tennis and fell backwards after reaching up to hit the tennis ball. Since then he has had gradually increasing falls, many backwards, mainly due to imbalance and inability to react quickly. He is now afraid to walk, especially as occasionally his feet will 'stick to the floor' and he is unable to move. This happens most frequently when he starts to walk or goes through a narrow space. On examination, he exhibits bilateral symmetric bradykinesia, axial and limb rigidity, vertical supranuclear gaze palsy, and difficulty moving his feet when first starting to walk or going through a doorway.
Diagnosis: Probable PSP with progressive gait freezing.
Explanation: The patient has a gradually progressive worsening of gait with falls and freezing of gait within the first three years of symptom onset (A1). With evidence of vertical supranuclear gaze palsy (01), he meets criteria for probable PSP-PGF.

Differential Diagnosis

The differential diagnosis of atypical parkinsonism is summarized in Table 11.3 (see also Fig. 11.1).

Table 11.2 Research diagnostic criteria for PSP with degree of diagnostic certainty (Hoglinger et al. 2017) [5]

Diagnostic certainty	Definition	Supporting clinical/ pathological observations	Predominant type	Terminology
Definite PSP	Gold standard defining the disease entity	Neuropathological diagnosis	Any clinical presentation	def. PSP
Probable PSP	Highly specific, but not very sensitive for PSP *Suitable for therapeutic and biological studies*	(01 or 02) + (P1 or P2)	PSP with Richardson's syndrome	prob. PSP-RS
		(01 or 02) + A1	PSP with progressive gait freezing	prob. PSP-PGF
		(01 or 02) + (A2 or A3)	PSP with predominant parkinsonism	prob. PSP-P
		(01 or 02) + C2	PSP with predominant frontal presentation	prob. PSP-F
Possible PSP	Substantially more sensitive, but less specific for PSP *Suitable for descriptive epidemiological studies and clinical care*	01	PSP with predominant ocular motor dysfunction	poss. PSP-OM
		02 + P3	PSP with Richardson's syndrome	poss. PSP-RS
		A1	PSP with progressive gait freezing	poss. PSP-PGF
		(01 or 02) + C1	PSP with predominant speech/language disorder[a]	poss. PSP-SL
		(01 or 02) + C3	PSP with predominant CBS[a]	poss. PSP-CBS
Suggestive of PSP	Suggestive of PSP, but not passing the threshold for possible or probable PSP *Suitable for early identification*	02 or 03	PSP with predominant ocular motor dysfunction	s.o. PSP-OM
		P1 or P2	PSP with predominant postural instability	s.o. PSP-PI
		03 + (P2 or P3)	PSP with Richardson's syndrome	s.o. PSP-RS
		(A2 or A3) + (03, P1, P2, C1, C2, CC1, CC2, CC3, or CC4)	PSP with predominant parkinsonism	s.o. PSP-P
		C1	PSP with predominant speech/language disorder	s.o. PSP-SL
		C2 + (03 or P3)	PSP with predominant frontal presentation	s.o. PSP-F
		C3	PSP with predominant CBS	s.o. PSP-CBS

The basic features B1+B2+B3 apply for all probable, possible, and suggestive criteria. Core clinical features are defined by their functional domain (ocular motor dysfunction [O], postural instability [P], akinesia [A], and cognitive dysfunction [C]), and stratified by presumed levels of certainty (1[highest], 2[mid], 3[lowest]) they contribute to the diagnosis of PSP

[a]Probable 4R-tauopathy (i.e., either PSP or CBD)

Table 11.3 Differential diagnosis of PSP, CBD, and MSA

Parkinson's disease
– Asymmetric onset of bradykinesia and 4–6 Hz rest tremor
– Marked and prolonged levodopa benefit
– Lack of early postural instability and falls
Dementia with Lewy bodies
– Hallucinations or delusions prior to the onset of parkinsonism
– Fluctuating levels of cognition with pronounced variations in attention and alertness
Alzheimer's disease
– Progressively worsening short-term memory loss with gradual onset of executive dysfunction, behavioral abnormalities, and cortical dementia
– Lack of prominent motor findings
Normal pressure hydrocephalus
– Subcortical dementia, urinary incontinence, wide-based magnetic gait
– Ventricular enlargement out of proportion to cortical atrophy
Vascular parkinsonism
– Multiple strokes, at least one involving the brainstem or basal ganglia
– Abrupt onset of symptoms without steady, progressive worsening
– Predominantly lower extremity parkinsonism
Frontotemporal dementia [50]
– Typical age of onset fourth to sixth decade
– Marked atrophy of frontal and temporal lobes on imaging
– 20–50% have first degree relative with FTD
Fragile X-associated Tremor/Ataxia Syndrome (FXTAS)
– Onset of ataxia, postural and kinetic tremor, parkinsonism, autonomic dysfunction, mild cognitive impairment with executive dysfunction, and peripheral neuropathy in males >50 years old
– May have family history of grandchild with Fragile-X syndrome or first degree relative with premature ovarian insufficiency (inability to get pregnant)
– MRI brain shows hyperintensity of middle cerebral peduncles (MCP sign) and white matter lesions
– Genetic testing shows premutation expansions (55–200 CGG repeats) in the fragile X mental retardation 1 (FMR1) gene
Spinocerebellar Ataxia ('SCA', types 1, 2, 3, 6, 7, 12, and 21)
– Lack of prominent autonomic dysfunction
– Young age of onset except SCA 6 (mean age of onset 55 y/o (range 31–77))
– Slowly progressive cerebellar ataxia
– Abnormal oculocephalic reflex
– Neuroimaging: Cerebellar and spinal cord atrophy, rarely with brainstem involvement
Creutzfeldt-Jakob disease
– Rapid progressive dementia (<1 year), myoclonus, akinetic mutism, extrapyramidal signs [8]

Treatment of PSP/Atypical Parkinsonism

Tables 11.4, 11.5, and 11.6 present the treatment of motor, non-motor, and neuropsychiatric symptoms of PSP/atypical parkinsonism.

Table 11.4 Treatment of motor symptoms of PSP

Motor symptoms
Parkinsonism (Bradykinesia, Rigidity, (rarely) Tremor)
• Trial of levodopa therapy
– Carbidopa-Levodopa (Sinemet) 25–100 mg up to two pills tid
Gradual titration is recommended to avoid side effects
– 25–33% of patients will have a significant, sustained response to levodopa therapy
– Dopamine agonists are generally avoided due to side effects and decreased efficacy
Postural instability/falls prevention
• Physical therapy
– Training focused on increasing amplitude of movements (i.e. LSVT-BIG) [51]
– Focus on postural stability/gait training
– Balance, eye movement, and visual awareness training may improve gait in PSP [52]
• Exercise
– Core strengthening
– Aerobic exercise (safe and as tolerated)
• Occupational therapy
– Home health assessment
– Evaluation for lifting devices or wheeled mobility aides
– Optimize upper limb function
• Assisted walking devices
– Cane, walker, wheelchair
Weighted walker may help prevent falls backwards
Freezing of gait
• Rasagiline (≤1 mg/day)
• Amantadine 100–200 mg bid (monitor for hallucinations or impaired cognition)
• Cues (focus on line on ground to step over)
– Weighted walker with laser light
Cervical or limb dystonia
• Botulinum toxin injections
• Oral medications (Trihexiphenidyl, Baclofen, Clonazepam) are less effective and generally avoided due to side effects
Eyelid dysfunction (blepharospasm or apraxia of eyelid opening)
• Botulinum toxin injections
• Oral medications are less effective
• Eyelid crutches may provide benefit

Table 11.5 Treatment of non-motor symptoms of PSP/atypical parkinsonism

Non-motor symptoms
Constipation
• High fiber diet
• Daily metamucil or prune juice
• Miralax (17 g once or twice daily as needed)
• Stool softeners (Colace)
Dream enactment behavior (RBD) and insomnia
• Melatonin
• Clonazepam (monitor for excessive sedation, impaired cognition)
Daytime somnolence
• Treat comorbid insomnia and sleep apnea
– Sleep study
– Continuous Positive Airway Pressure (CPAP)/Bivalve Positive Airway Pressure (BiPAP)
• Modafinil (Provigil™)
Sialorrhea
• Botulinum toxin injections
• Glycopyrrolate (monitor for impaired cogntion or balance)
Dysphagia
• Speech therapy
– Bedside swallow evaluation
– Modified barium swallow study
• Monitoring swallow function
• Eating and drinking strategies
– Tuck chin while eating/drinking
– Modified diet and fluids
– Maintaining oral hygiene
– Assistive mealtime devices
• Discussion regarding placement of Percutaneous Endoscopic Gastrotomy (PEG) feeding tube

Table 11.6 Treatment of neuropsychiatric symptoms in PSP/atypical parkinsonism

Neuropsychiatric symptoms
Depression/anxiety
• Antidepressant
– Recommend Selective Serotonin Reuptake Inhibitor (SSRI) or Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)
Avoid tricyclic antidepressants due to potential side effects
Pseudobulbar affect
• Dextromethorphan/Quinidine (Nuedexta™)

Corticobasal Degeneration

Introduction

Corticobasal degeneration (CBD) is a pathologic diagnosis which encompasses the clinical phenotypes of corticobasal syndrome (CBS), frontal behavioral-spatial syndrome (FBS), nonfluent-agrammatic variant of primary progressive aphasia (naPPA or NAV), and progressive supranuclear palsy syndrome (PSPS, a subtype of CBD with overlapping features of CBS and PSP) [24]. There is significant variation and overlap between these subtypes, with features of each seen as the disease progresses. CBD, along with PSP, is a four-repeat tauopathy classified as a sporadic form of atypical parkinsonism.

Clinical Manifestations

History

CBD rarely manifests before 50 years of age, and the mean age at onset is 60 years ± 9.7 years [25]. Patients may develop cognitive, language, or behavioral changes before the onset of motor symptoms, leading to a misdiagnosis of Alzheimer's disease or frontotemporal dementia until approximately 3 years after symptom onset [2]. Initial motor symptoms of CBS include markedly asymmetric upper limb bradykinesia, rigidity, dystonia, and myoclonus [1]. Limb apraxia is pronounced in CBD—patients often describe an inability to perform gross or fine motor movements with the affected limb. Asymmetric "hand clumsiness" is the most common presenting symptom, seen in approximately 50% of patients. [2].

Based on a large series of pathologically confirmed cases of CBD, the most common abnormalities of higher cortical function include cognitive impairment, behavioral changes, limb apraxia, aphasia, depression, cortical sensory loss, and alien limb phenomenon. The most common motor findings include unilateral limb rigidity, bradykinesia/clumsy limb, postural instability, falls, abnormal gait, axial rigidity, tremor, limb dystonia, and myoclonus [24].

Speech difficulties are common in CBD, with dysarthria and progressive aphasia being the most common disturbances [24]. Nonfluent aphasia typically accompanies right sided motoric symptoms, while visuospatial deficits are associated with left sided motoric symptoms [1]. Left sided motoric symptoms are also more commonly associated with the 'alien limb' phenomenon (involuntary limb movements accompanied by a sensation that the limb had a will of its own), indicative of right parietal lobe involvement [26].

As with other forms of atypical parkinsonism, CBD progresses rapidly. Mean duration from symptom onset to death ranges from 5.5 to 7.9 years in various studies [27, 28]. Death is usually secondary to pulmonary complications or sepsis in the setting of prolonged immobility [27].

Physical Examination

Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetition [1]. Unilateral limb rigidity (clinically assessed by passive movement of the wrists, elbows, knees, and ankles) is prominent in the affected upper limb, while lower limb and eventually axial rigidity tend to occur later in the course of the disease [24]. Tremor and focal myoclonus are both seen in CBD, the latter characterized by irregular, non-rhythmic jerking motions of extremities, most commonly induced by touch ('stimulus-sensitive myoclonus') [2, 24].

The combination of upper limb rigidity and dystonia at rest often presents as arm elevation, while the affected upper limb is often flexed and held against the body during ambulation. Aside from minimal to no arm swing in the affected limb, the gait in CBD resembles the 'shuffling gait' seen in PD, due to decreased stride length and diminished step amplitude [29]. Postural instability is assessed by the "pull test" (patients stand with feet apart and are pulled backwards at the shoulders by the examiner). Severe postural instability should alert the examiner for the possibility of the PSPS phenotype of CBD.

Oculomotor abnormalities in CBD are common and include saccadic rather than smooth pursuit [30]. Slowing of vertical saccades and vertical supranuclear gaze palsy are rare except in the PSPS phenotype of CBD.

Specific tests should be performed to evaluate for abnormalities of higher cortical function. Ideomotor apraxia (inability to perform goal-oriented movements) is tested by asking patients to imitate simple motions (such as giving a 'thumbs up'). Ideational apraxia (inability to coordinate sequential motor movements) is tested by showing pictures of common objects, such as a comb, and asking the patient to pantomime their use [31]. Cortical sensory loss may manifest as agraphesthesia (inability to recognize numbers or letters written on one's palm), astereognosis (inability to identify a common object when placed in the affected hand with eyes closed), or extinction (intact sensation of the affected limb unless touching the opposite limb at the same time) [32–34].

Cognitive assessment via MoCA or MMSE typically demonstrates deficits in attention and visuospatial domains, with executive dysfunction most pronounced in the FBS phenotype of CBD [24].

Diagnostic Approach for CBD

The clinical diagnosis of CBD is based primarily on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. The essential features of CBD are summarized here (see also Fig. 11.1 and Tables 11.3, 11.7, 11.8).

History

- Lateralized difficulty using upper limb often described as “hand clumsiness”
- Gradual onset of asymmetric parkinsonism (bradykinesia, rigidity, less commonly tremor)
- Progressive language, cognitive, and behavioral decline
- Rapid onset and progression of symptoms
- Limited or no response from levodopa

Physical Exam

- Striking asymmetry, initially involving upper limb
- Apraxia (most commonly ideational, with ideomotor apraxia seen in later stages)
- Cortical sensory loss consisting of agraphesthesia, astereognosis, or extinction
- Minimal to absent arm movement of involved limb on gait assessment
- Upper limb rigidity and dystonia contributing to arm levitation at rest
- Focal myoclonus that is most commonly stimulus-sensitive
- Deficits in attention and visuospatial domains, as well as executive function

Imaging

MRI Brain or CT Head (Fig. 11.4)

Although imaging findings vary based on the CBD phenotype, there is typically asymmetric atrophy of the posterior frontal and parietal lobes, along with dilatation of the lateral ventricles in the affected hemisphere [35].

DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

FDG-PET Scan

- Hypometabolism in the frontal, parietal lobes, and subcortical structures (thalamus, caudate nucleus, and putamen), with marked asymmetry between the two hemispheres [36]

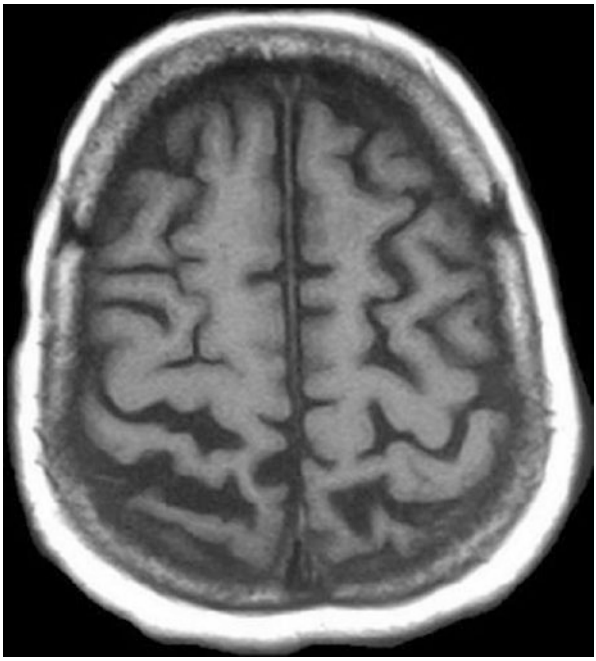

Fig. 11.4 Asymmetric (*right*) parietal lobe atrophy indicative of CBD

Laboratory

- Blood tests are typically of limited utility in diagnosing CBD
- CSF biomarkers are promising but need further validation

Genetic Testing

- Genetic testing is unnecessary as virtually all cases of CBD are sporadic

Pathology

- Definitive diagnosis of CBD can only be made by pathologic analysis upon autopsy**.** Pathologically, CBD is characterized by tau-positive neuronal and glial lesions in the cortex and striatum, particularly astrocytic plaques and thread-like lesions in both white matter and gray matter. Neuronal loss is also seen in focal cortical regions and in the substantia nigra [37]

Diagnostic Criteria

Corticobasal degeneration remains a neuropathologic diagnosis performed at autopsy. Clinical diagnostic criteria to incorporate the most common phenotypes associated with CBD were recently developed (Table 11.7, 11.8) [24].

Differential Diagnosis

The differential diagnosis of PSP, CBD, and MSA is shown in Fig. 11.1 and Table 11.3.

Therapeutics (Treatment Care Path)

The therapeutic approach to atypical parkinsonism including CBD is shown in Tables 11.4, 11.5, and 11.6.

Table 11.7 Proposed clinical phenotypes (syndromes) associated with the pathology of corticobasal degeneration

Clinical phenotype	Features
Probable corticobasal syndrome	Asymmetric presentation of two of: (a) limb rigidity or akinesia, (b) limb dystonia, (c) limb myoclonus plus two of: (d) orobuccal or limb apraxia, (e) cortical sensory deficit, (f) alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: one of: (a) limb rigidity or akinesia, (b) limb dystonia, (c) limb myoclonus plus one of: (d) orobuccal or limb apraxia, (e) cortical sensory deficit, (f) alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of: (a) executive dysfunction, (b) behavioral or personality changes, (c) visuospatial deficits
Nonfluent/agrammatic variant of primary progressive aphasia	Effortful, agrammatic speech plus at least one of: (a) impaired grammar/sentence comprehension with relatively preserved single word comprehension, or (b) groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of: (a) axial or symmetric limb rigidity or akinesia, (b) postural instability or falls, (c) urinary incontinence, (d) behavioral changes, (e) supranuclear vertical gaze palsy or decreased velocity of vertical saccades

Adapted from Armstrong, et al. 2013 [24]

Table 11.8 Diagnostic criteria for corticobasal degeneration

	Clinical research criteria for probable sporadic CBD	Clinical research criteria for possible sporadic CBD
Presentation	Insidious onset and gradual progression	Insidious onset and gradual progression
Minimum duration of symptoms	1 year	1 year
Age at onset	≥50 years old	≥50 years old
Family history (two or more relatives)	Exclusion	Permitted
Permitted phenotypes	1. Probable CBD or 2. FBS or NAV plus at least one CBD feature: • Limb rigidity or akinesia • Limb dystonia • Limb myoclonus • Orobuccal or limb apraxia • Cortical sensory deficit • Alien limb phenomena	1. Possible CBD or 2. FBS or NAV or 3. PSPS plus at least one CBD feature: • Limb dystonia • Limb myoclonus • Orobuccal or limb apraxia • Cortical sensory deficit • Alien limb phenomena
Genetic mutation affecting tau (eg, MAPT)	Exclusion	Permitted
Exclusion options	• Evidence of Lewy body disease: classic 4 Hz Parkinson's disease resting tremor, excellent and sustained levodopa response, or hallucinations. • Evidence of multiple system atrophy: dysautonomia or prominent cerebellar signs. • Evidence of amyotrophic lateral sclerosis: presence of both upper and lower motor neuron signs. • Semantic- or logopenic-variant primary progressive aphasia. • Structural lesion suggestive of focal cause. • Granulin mutation or reduced plasma progranulin levels; TDP-43 mutations; FUS mutations. • Evidence of Alzheimer's disease, such as low cerebrospinal fluid beta-amyloid 42-to-tau ratio or positive ^{11}C-Pittsburgh compound B PET; or genetic mutation suggesting Alzheimer's disease (eg, presenilin, amyloid precursor protein).	Same as probable CBS

Adapted from Armstrong, et al. 2013 [24]
CBD corticobasal degeneration, *CBS* corticobasal syndrome, *FBS* frontal behavioral-spatial syndrome, *MAPT* microtubule-associated protein tau, *NAV* nonfluent/agrammatic variant of primary progressive aphasia, *PSPS* progressive supranuclear palsy syndrome

Multiple System Atrophy

Introduction

Multiple System Atrophy (MSA) is a sporadic adult-onset neurodegenerative disorder consisting of autonomic failure and varying degrees of parkinsonism or cerebellar ataxia. Recently revised diagnostic criteria identifies two forms of MSA, both of which require autonomic dysfunction for diagnosis: MSA presenting with predominant parkinsonism (MSA-P; also known as "striatonigral degeneration") or with predominant cerebellar ataxia (MSA-C; also known as "olivopontocerebellar atrophy") [38]. Parkinsonism with early severe dysautonomia, cerebellar symptoms, gait disturbance, and lack of early cognitive impairment are most predictive of MSA [39].

Clinical Manifestations

History

The onset of MSA is generally in the sixth decade, and the disease rarely if ever presents before 30 years or after 75 years [2].

The initial symptom in males is typically erectile dysfunction, while most patients present to a physician with urinary disturbances (consisting of urgency, frequency, nocturia, incomplete bladder emptying, and incontinence) [40]. Other autonomic symptoms include orthostatic hypotension, "cold hands and feet" (Raynaud phenomenon), respiratory dysfunction (sleep apnea, inspiratory stridor), cardiac arrhythmia, and constipation.

Motor symptoms, consisting of parkinsonism (bradykinesia and rigidity, tremor, or postural instability) and/or cerebellar ataxia, typically develop after the onset of dysautonomia.

In contrast to Parkinson's disease, motor symptoms tend to progress rapidly, and only approximately 30% of MSA patients have a clinically significant response to levodopa [1]. Bulbar dysfunction manifesting as dysphonia, dysarthria, and dysphagia is a prominent and rapidly progressing feature of MSA [41].

Although prominent cognition dysfunction is not an early feature of MSA, most patients eventually develop prefrontal dysfunction, which is more frequent and severe in MSA-P than MSA-C [42]. Pseudobulbar affect with emotional incontinence (inappropriate laughing or crying) is seen more commonly than in Parkinson's disease.

The symptoms of MSA progress rapidly, and most patients become wheelchair bound within 5 years of symptom onset [41]. The median survival is 7–10 years (although wider ranges have been reported), and predominant cerebellar features and a younger age of onset (<60) predict a slightly better prognosis. Death is most commonly due to aspiration, sleep apnea, or cardiac arrhythmia [43].

Physical Examination

Standard clinical assessment of patients with suspected MSA should include general neurologic examination with focus on evaluation for pyramidal and Parkinsonian signs, cognitive testing and orthostatic vital signs.

Patients with bradykinesia demonstrate delayed initiation of movement, progressive slowing, and/or decrement in amplitude with repetitive movement of the hands, legs or feet [1]. Bradykinesia and rigidity are typically more symmetric in MSA than in PD. Resting tremor is infrequently seen in MSA (found in 13–29% of patients. [43, 44]. Patients are assessed for tremor at rest, with arms outstretched (postural tremor), and with movement (kinetic tremor). Postural and kinetic tremor, as well as stimulus-sensitive myoclonus (irregular twitching movements elicited by tapping on the patients fingers with their arms outstretched and palms facing up) are seen more commonly [1].

Cerebellar dysfunction manifests on examination most commonly as a wide-based, ataxic gait with severe postural instability (assessed by the "pull test", patients stand with feet apart and are pulled backwards at the shoulders by the examiner). Limb ataxia is seen less frequently, but can be a prominent feature of MSA-C. Cerebellar oculomotor dysfunction can present as nystagmus, square wave jerks, jerky pursuit, and dysmetric saccades (in contrast to the slowing of vertical saccades and decreased range of extraocular movements in PSP) [38]. Patients most commonly present with a mixed cerebellar dysarthria with combinations of hypokinetic, ataxic, and spastic components of speech [45].

Dystonia is a frequent feature of MSA if anterocollis (forward flexion of the neck) is considered a form of cervical dystonia. Laryngeal dystonia manifesting as inspiratory stridor can occur, and levodopa therapy may result in facial and oromandibular dystonia [2]. Abnormal contractures of the hands and feet may be seen on examination, and patients may present with cold, violaceous extremities. The "Pisa syndrome" (severe lateral flexion of the spine causing the patient to lean sideways) or camptocormia (severe anterior flexion of the spine) may present as well [41].

Degeneration of the corticospinal tracts in MSA may manifest as pyramidal signs including spasticity, hyperreflexia, and the Babinski sign [46].

Cognition is typically assessed via MoCA or MMSE. Patients with MSA-P exhibit executive dysfunction with severe involvement of verbal fluency, visuospatial and constructional function. Cognitive impairment is milder in MSA-C, generally impacting only visuospatial and constructional function [42].

Orthostatic Vital Signs

Blood pressure and heart rate are assessed after the patient lies supine for at least 3 min, then again 3 min after standing. Diagnostic criteria for MSA defines orthostatic hypotension as a drop in blood pressure of at least 30 mm Hg or of diastolic blood pressure by at least 15 mm Hg with an undefined compensatory increase in heart rate [38].

Diagnostic Approach for MSA

The clinical diagnosis of MSA is primarily based on history and physical examination, with supportive evidence provided by imaging. The definitive diagnosis is based on pathologic confirmation at autopsy. The key features of MSA are shown here:

History

- Early severe autonomic dysfunction (erectile dysfunction, urinary disturbances, lightheadedness upon standing, respiratory difficulty, constipation, and/or cardiac arrhythmias)
- Rapid progression of parkinsonism (that is rarely responsive to levodopa) or cerebellar ataxia
- Postural instability and early falls (30 months after symptom onset on average) [9]
- Limited cognitive impairment relative to other forms of parkinsonism
- Lack of family history of similar symptoms

Neurologic Examination

- Orthostatic hypotension
- Typically bilateral and symmetric bradykinesia and rigidity
- Postural and kinetic irregular tremor (more common than resting tremor)
- Stimulus sensitive myoclonus
- Cerebellar features (wide-based ataxic gait, limb ataxia, oculomotor dysfunction, and dysarthria)
- Anterocollis, forward or sideward flexion of the spine, abnormal contractures of the hands or feet
- Cold hands and feet, with a dusky, purplish discoloration
- Pyramidal signs

Laboratory Testing

- Lab values are typically of limited utility in diagnosing MSA

Imaging

MRI Brain

- MSA-P and MSA-C:
  - Pontine and cerebellar atrophy involving the vermis and hemispheres (more common and severe in MSA-C) (Fig. 11.5) [47]

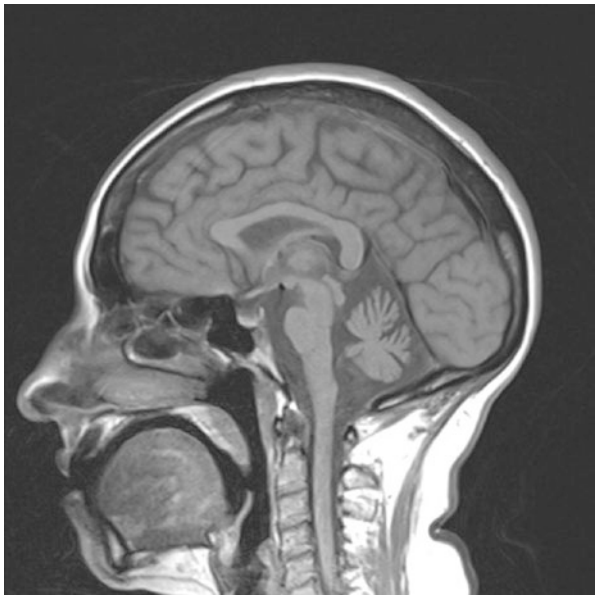

Fig. 11.5 Pontine and cerebellar atrophy in MSA-C

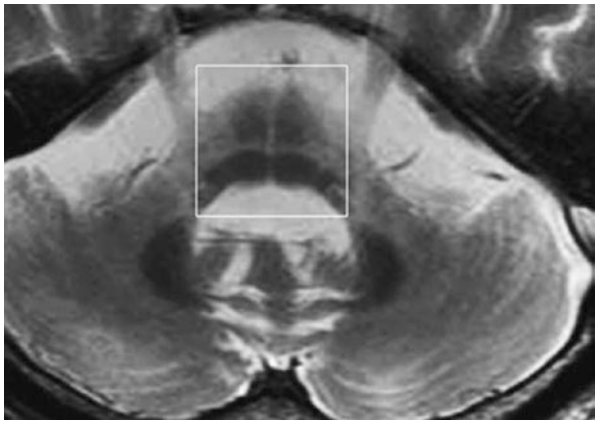

Fig. 11.6 "Hot Cross Bun" sign in MSA

  - "Hot-cross bun" sign: cross-like degeneration of pontine fibers secondary to brainstem atrophy (Fig. 11.6)

- MSA-P (rarely MSA-C):
  - Putaminal atrophy and occasionally T2 hypointensity in the posterolateral putamen with slit-like hyperintensity of the surrounding rim [48]

DaT Scan

- FDA indicated for detecting loss of functional dopaminergic neuron terminals in the striatum [21]
- Reduced uptake is indicative of Parkinsonism, but does not differentiate PD, PSP, CBD, MSA, or DLB

FDG-PET Scan

- Hypometabolism in the putamen, brainstem, or cerebellum [38]

Genetic Testing

- Genetic testing is unnecessary as virtually all cases of MSA are sporadic

Ancillary Testing

- Cardiovascular and sudomotor autonomic testing may aid in differentiating MSA from PD and other adult onset cerebellar ataxias
- Urologic evaluation and urodynamic testing to identify the type of neurogenic bladder dysfunction
- Sleep study to evaluate for obstructive sleep apnea, nocturnal inspiratory stridor, and REM behavioral disorder (RBD)
- Cardiologic evaluation of arrhythmia and/or refractory orthostatic hypotension

Pathology

Diagnosis of definite MSA can only be made by pathologic analysis on autopsy. Pathologically, MSA is characterized by alpha-synuclein glial cytoplasmic inclusions leading to degeneration of striatonigral or olivopontocerebellar structures [49]. Definite MSA remains a neuropathologic diagnosis with features described above. Recently revised diagnostic criteria for the diagnosis of probable MSA (Table 11.9) and possible MSA (Table 11.10) are shown below.

Table 11.9 Criteria for the diagnosis of probable MSA

A sporadic, progressive, adult onset (>30 years/o) disease characterized by
Autonomic failure involving urinary incontinence (inability to control the release of urine from the bladder, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic
Plus either of the following
Poorly levodopa-responsive parkinsonism (bradykinesia with rigidity, tremor, or postural instability)
A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Adapted from Gilman, et al. [38]

Table 11.10 Criteria for the diagnosis of possible MSA

A sporadic, progressive, adult onset (>30 years/o) disease characterized by
≥1 of the following features suggesting autonomic dysfunction: Otherwise unexplained urinary urgency, frequency or incomplete bladder emptying, erectile dysfunction in males, or significant orthostatic blood pressure decline that does not meet the level required in probable MSA *and*
≥1 of the following additional features: *Possible MSA-P or MSA-C*: – Babinski sign with hyperreflexia – Stridor *Possible MSA-P:* – Rapidly progressive parkinsonism – Poor response to levodopa – Postural instability within 3 y of motor onset – Gait ataxia, cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction – Dysphagia within 5 y of motor onset – Atrophy on MRI of putamen, middle cerebellar peduncle, pons, or cerebellum – Hypometabolism on FDG-PET in putamen, brainstem, or cerebellum *Possible MSA-C*: – Parkinsonism (bradykinesia and rigidity) – Atrophy on MRI of putamen, middle cerebellar peduncle, or pons – Hypometabolism on FDG-PET in putamen – Presynaptic nigrostriatal dopaminergic denervation on SPECT or PET
Plus either of the following
Parkinsonism (bradykinesia with rigidity, tremor, or postural instability)
A cerebellar syndrome (gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction)

Adapted from Gilman, et al. [38]

Differential Diagnosis

The differential diagnosis of MSA is shown in Fig. 11.1 and Table 11.3.

Therapeutics (Treatment Care Path)

The treatment approach to MSA atypical parkinsonism is shown in Tables 11.4, 11.5, and 11.6. The treatment algorithm for symptomatic neurogenic orthostatic hypotension is shown in Fig. 11.7.

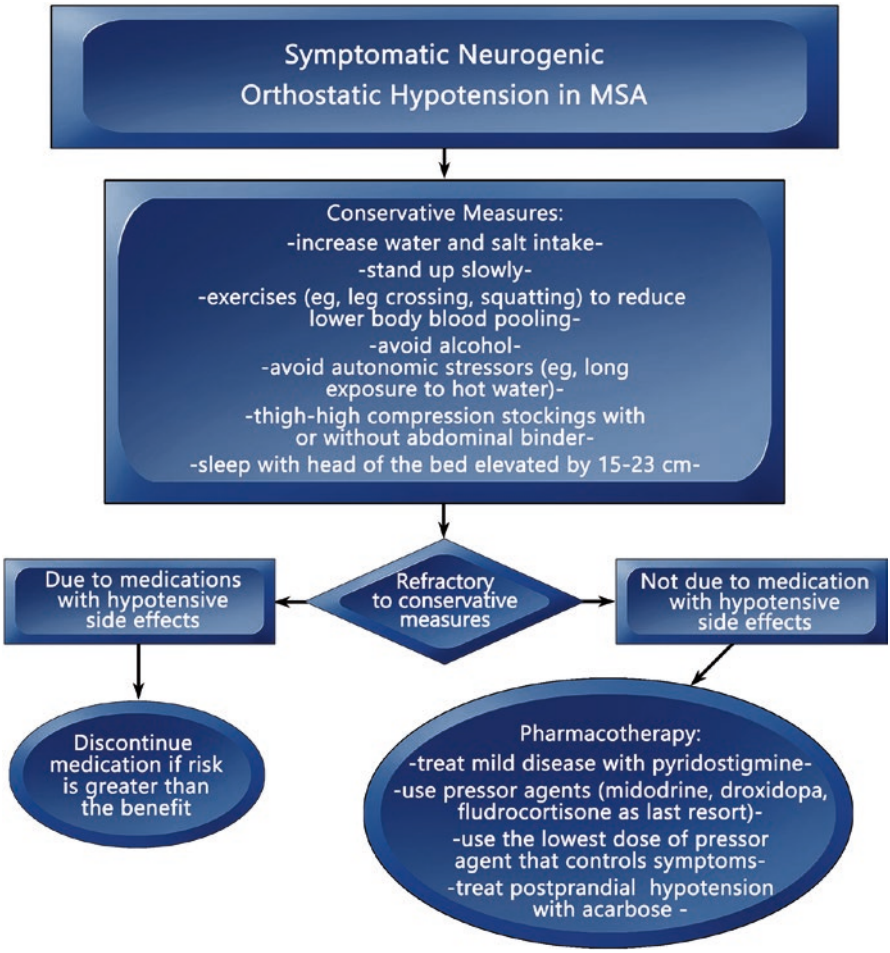

Fig. 11.7 Treatment algorithm for symptomatic neurogenic orthostatic hypotension

ICD 10 Codes

MSA Diagnosis: G90.3
PSP Diagnosis: G23.1
CBD Diagnosis: G31.85

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