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Exploring bedside clinical features of parkinsonism: A focus on differential diagnosis

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ABSTRACT

The proper diagnosis of parkinsonian disorders usually involves three steps: identifying core features of parkinsonism; excluding other causes; and collating supportive evidence based on clinical signs or investigations. While the recognition of cardinal parkinsonian features is usually straightforward, the appreciation of clinical features suggestive of specific parkinsonian disorders can be challenging, and often requires greater experience and skills. In this review, we outline the clinical features that are relevant to the differential diagnosis of common neurodegenerative parkinsonian disorders, including Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. We aim to make this process relatable to clinicians-in-practice, therefore, have categorised the list of clinical features into groups according to the typical sequence on how clinicians would elicit them during the examination, starting with observation of facial expression and clinical signs of the face, spotting eye movement abnormalities, examination of tremors and jerky limb movements, and finally, examination of posture and gait dysfunction. This review is not intended to be comprehensive. Rather, we have focused on the most common clinical signs that are potentially key to making the correct diagnosis and those that do not require special skills or training for interpretation. Evidence is also provided, where available, such as diagnostic criteria, consensus statements, clinicopathological studies or large multi-centre registries. Pitfalls are also discussed when relevant to the diagnosis. While no clinical signs are pathognomonic for certain parkinsonian disorders, certain clinical clues may assist in narrowing a differential diagnosis and tailoring focused investigations for the individual patient.

1. Introduction

Parkinsonism is a syndrome presenting with a combination of four cardinal features: bradykinesia, tremor-at-rest, rigidity, and loss of postural reflexes [1]. The combination of these signs at different levels constitutes clinically defined 'definite', 'probable', and 'possible' parkinsonism. While these features are non-diagnostic by themselves, most clinical diagnostic criteria of parkinsonian disorders generally require, as the initial step, the presence of combinations of these cardinal features. Moreover, the presence of certain cardinal features can be used as supportive features of a particular parkinsonian disorder or considered as a non-supporting feature of others. A good example is the classic pill-rolling rest tremor, which is included in the second consensus statement as a non-supporting feature of multiple system atrophy (MSA) while being regarded as one of the supportive prospective criteria for Parkinson's disease (PD) [2,3].

To clinically diagnose a parkinsonian disorder, clinicians need to establish more than just the presence of a parkinsonian syndrome, and a focused examination is often required to demonstrate relevant clinical signs that narrows down the differential diagnosis. Clinical features of parkinsonism are not limited to the four above-mentioned cardinal features. Rather, a full spectrum of signs involving different systems, such as oculomotor function, musculoskeletal system, sleep, autonomic function, sensory, cognition and behaviour, are often appreciated by the astute clinician. The term 'parkinsonism-plus syndrome' has been used in the medical literature to denote the presence of non-cardinal

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Table 1
Comparison of bedside clinical features amongst patients with common neurodegenerative parkinsonisms.

Bedside clinical features	Parkinson's disease	Multiple system atrophy	Progressive supranuclear palsy	Corticobasal degeneration
Facial expression and clinical signs of the face				
Hypomimia	Presence	Presence	Presence	Presence
Masked/poker face	+ + +	N/A	N/A	N/A
Nasolabial fold	Flattened	N/A	Deepened	N/A
Reduced spontaneous blink rates	+	+ +	+ + +	N/A
Slow blink rates	+ +	+ +	+ + +	N/A
Procerus sign, corrugator sign, or vertical wrinkling of the forehead sign	–	+/-	+ + +	N/A
Reptilian stare or a surprised and astonished facial expression	–	–	+ + +	N/A
Blepharospasm	+/-	+ +	+ + +	+
Apraxia of eyelid opening (AEO)	N/A	N/A	+ + +	+
Eye movement abnormalities				
Slowing of downward saccade	–	+/-	+ + +	+/−
Supranuclear gaze palsy	+/−	+/-	+ + +	+/−
Blink or trust their heads towards the target before making a saccade	–	–	+ + +	+/−
Round the Houses sign	–	–	+ + +	N/A
Square wave jerks (SWJs)	+/−	+ +	+ + +	+/−
Gaze-evoked, downbeat, and rebound nystagmus	–	+ + +	+/-	+/−
Impaired smooth pursuit	+	+ + +	+	+/−
Increased saccadic latency	N/A	N/A	N/A	+ + +
Orofacial dystonia	+/−	+ +	+	+
Tremor and jerky hand movements				
Resting tremor (Pill-rolling tremor)	+ + +	+ + (MSA-P subtype)	+ (PSP-P subtype)	N/A
Re-emerging tremor	+ + +	–	–	–
Jerky postural tremor (minipolymyoclonus)	N/A	+ + +	+	+
Posture and gait abnormalities				
Camptocormia	+ +	+ + +	N/A	N/A
Antecollis	+	+ + +	N/A	N/A
Retrocollis	–	–	+ + +	–
Lateral trunk flexion or Pisa syndrome	+ +	+ + +	N/A	N/A
Early falls	+	+ +	+ + +	N/A
Narrow-based stance	+ + +	–	–	N/A
Freezing of gait (FOG)	+ + +	+ + +	+ + +	+/−
Backward falls	+	+	+ + +	+/−
Drop down falls	+	+ + +	+/−	N/A

+ + +: frequently reported; + +: occasionally reported; +: had been reported in a case series; +/−: may be observed; -: never been reported; N/A: Data not available; MSA-P: Multiple system atrophy-parkinsonian subtype; PSP-P: Progressive supranuclear palsy-parkinsonism subtype.

features of parkinsonism that exist in non-PD neurodegenerative parkinsonisms [4]. In a formal knowledge-based questionnaire assessment, diagnostic differentiation of parkinsonism was identified as a common knowledge gap amongst internists and general practitioners who usually have the first contact with patients [5]. The inability to recognise 'plus' features may be one of many reasons why atypical parkinsonian disorders (APDs) are found to be frequently underdiagnosed by general neurologists [6]. Physicians may also be challenged when presented with particular clinical features that are unfamiliar to them. To assist physicians in narrowing their differential diagnosis, a stepwise approach has been proposed: first verify a parkinsonian syndrome, then search for clinical signs that provide clues to a specific parkinsonian disorder, and then finally consider ancillary tests that establish the diagnosis [7]. In this article, we aim to highlight certain clinical features that are relevant in the diagnostic work-up of parkinsonian patients, especially amongst the common neurodegenerative parkinsonian disorders, including PD, MSA, progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Although further subtypes of parkinsonian disorders are increasingly being recognised, our review is limited to the discussion of the clinical signs seen in the most typical or common presentations of these parkinsonian disorders. For example, we interpret the clinical signs of PSP in the context of Richardson's syndrome (RS), not inclusive of other subtypes of PSP; and the term 'CBD' is used within the context of corticobasal syndrome (CBS) phenotype [8,9]. We aim to make this article user-friendly for clinicians, therefore, we have categorised the list of clinical features according to how clinicians would typically elicit them during an examination, starting with observation of facial expression and clinical signs of the face, spotting eye movement abnormalities, limb examination, and examination of posture and gait (Table 1).

2. Facial expression and clinical signs of the face

Observation of facial expression is often the first part of the examination clinicians perform upon meeting their patients. A lot of information can be gained from just observing facial expression or looking for specific clinical signs on a patient's face. In fact, experienced clinicians may be able to make an initial diagnosis as soon as patients walk into the examination room based on such patterned recognition. While a reduction or loss of spontaneous facial movements and emotional facial expression, termed 'hypomimia', is a common feature described in patients with PD and APDs, certain facial characteristics have been studied and can be used to differentiate between various forms of parkinsonian disorders [10].

2.1. Facial expression

Although facial features are not considered as part of validated diagnostic criteria of PD and APDs, the presence and severity of hypomimia is included in the motor section of the Unified Parkinson's

Fig. 1. Distinguished facial features amongst patients with parkinsonism. 1A: Typical mask or poker face in a patient with Parkinson's disease, characterised by widened palpebral fissures, associated with flattened nasolabial folds and reduced wrinkles around the orbicularis oris; 1B: Vertical wrinkling of the forehead in a patient with Richardson's syndrome; 1C: 'Reptilian stare' in a patient with progressive supranuclear palsy, characterised by progressive widening of the eyebrow along with lid retraction; 1D: Blepharospasm, the most common form of focal dystonia in progressive supranuclear palsy; 1E: Apraxia of eyelid opening in a patient with progressive supranuclear palsy, demonstrated by difficulty in eyelid opening, partially compensated by frontalis muscle hyperactivation; 1F: Typical orofacial dystonia in a patient with probable multiple system atrophy.

Disease Rating Scale (UPDRS) and Unified Multiple System Atrophy Rating Scale (UMSARS); whereas eyelid function, but not whole facial expression, is included in the ocular motor section in the PSP Rating Scale (PSPRS) [11–13]. Overall, while hypomimia has been described as a feature in PD, MSA, and PSP, studies comparing facial characters between PD and APDs are limited. Based on general descriptions, facial expression amongst PD patients resembles that of a person without interest in the surrounding environment, so called 'masked/poker' face. In one study, compared to PD, hypomimia was reported to be more common in MSA at both the baseline and 62-month visits [14]. Indeed, the face-speech item was considered as an independent factor accounting for > 70% of the variance in both PD and MSA patients.

Hypomimia in PD is characterised by widened palpebral fissures, associated with flattened nasolabial folds and reduced wrinkles around the orbicularis oris, resulting in unintentionally opened mouth (Fig. 1A) [15]. However, decreased palpebral fissure was found to be more prevalent amongst PD patients than control subjects, coinciding with the side of initial parkinsonian involvement [16]. More importantly, some differences in the features of hypomimia between PD and APDs may provide clues for clinicians in making a differentiation (Fig. 1A–F). In contrast to the flattened nasolabial folds in PD, they are usually deepened in PSP patients [17]. While spontaneous blink rates are all reduced in PD, PSP and MSA patients except in the presence of blepharospasm, blink rate is much slower in PSP compared to PD (3/min vs. 12.5/min, respectively) [18–22]. Additionally, while eyelid movements are of normal amplitude and velocity in PD, slower blinks have been observed in PSP [23].

2.2. Clinical signs of the face

Certain facial features may be used for clinical differentiation of parkinsonism, primarily based on patterns of facial dystonia that are frequently reported amongst patients with APDs. Dystonic vertical wrinkles in the glabellar region and bridge of the nose secondary to contraction of the frontalis, procerus and corrugator muscles have been reported in patients with PSP, referred to using different names, including procerus sign, corrugator sign, or vertical wrinkling of the forehead sign (Fig. 1B) [17,24,25]. Interestingly, this sign was first recognised by Charles Darwin in 1872 using the term 'Omega's sign' of melancholia in patients with major depressive disorder and psychomotor agitation [26]. Indeed, when studied prospectively in patients with parkinsonism, the presence of vertical wrinkling of the forehead was significantly observed in PSP, but not PD or MSA patients [25]. Only one out of six MSA patients in this series were observed to have this sign. In addition, it can also be used to differentiate between patients with PD and PSP-parkinsonism (PSP-P). Progressive widening of the eyebrow, possibly as a result of lid retraction, may result in a widening of palpebral fissures, resulting in the 'reptilian' stare or surprised and astonished facial expression, observed amongst PSP (Fig. 1C) [23]. Blepharospasm is reported to be most prevalent in PSP (70%), and is much less common in other forms of APDs (8–11% in MSA) and even rarer in PD (0.9%) [27,28]. However, its significance for clinical differentiation remains unclear (Fig. 1D). Perhaps, it is the presence of apraxia of eyelid opening (AEO) with parkinsonism that carries greater diagnostic value for PSP (Fig. 1E) [28]. In a study involving over 1100 patients with parkinsonism, AEO usually coexisted with blepharospasm, and isolated AEO was not identified [27].

Examination of the lower face can also provide some diagnostic clues, particularly in APDs. One of the supporting features of MSA is orofacial dystonia, characterised by spontaneous, sustained and frequently asymmetrical (or even unilateral) dystonia of orofacial and platysma muscles, resembling the well-known risus sardonicus of tetanus (Fig. 1F) [2,29,30].

3. Eye movement abnormalities

In patients with neurodegenerative parkinsonisms, oculomotor signs can be key to making a diagnosis. Therefore, careful clinical examination of eye movements is an invaluable adjunct to standard neurological assessments. Among various types of eye movement examination, fixation, vestibulo-ocular reflexes (VORs), and saccades are of particular interest because the close link between these eye movements and brainstem function, which is predominantly affected in patients with neurodegenerative parkinsonisms; and attention, which is likely to be

disturbed by cognitive impairments associated with these disorders [31,32]. While mild impairments of eye movements can be observed with normal ageing, the focus in this section is on distinctive eye movement features that are relevant for differential diagnosis of neurodegenerative parkinsonisms. In most cases, clinical oculomotor examination is usually adequate, and adjunctive laboratory eye movement measurement do not usually add more information for eliciting a differential diagnosis.

3.1. Abnormalities of saccades and pursuit

Although eye movement abnormalities can be detected in PD patients, even at the early stages, they are generally subtle, comprising of mild hypometria of voluntary, particularly upward saccades and mildly impaired smooth pursuit [33,34]. These abnormalities, by themselves, are non-specific, and therefore, have minimal diagnostic significance. What is relevant in clinical practice is when clinicians identify *other* eye movement abnormalities in patients whom they initially thought had PD. Those findings should prompt clinicians to perhaps consider an alternative diagnosis of APDs. Indeed, oculomotor dysfunction has been identified as one of the four main clinical features that predicts PSP pathology [35]. Slowing of downward saccades is considered the hallmark of RS, and is included in the diagnostic criteria of PSP [36–38]. Indeed, the velocity of upward vertical saccades is also reduced and upward gaze palsy is usually identified more frequently than downgaze gaze palsy in patients with RS [39]. Horizontal saccadic slowing develops later, and most patients with RS eventually lose the ability to perform saccades and smooth pursuit, which is largely overcome by the VOR, thus indicating a 'supranuclear gaze palsy' [37]. The evolution of eye movement abnormalities in RS emphasises the importance of determining saccadic velocity, not only gaze palsy, in patients who physicians are suspicious of having PSP. In two series of pathologically proven cases of PSP, not all patients were documented to have vertical gaze palsy at the time of diagnosis [40,41]. Clinical detection of mildly slow saccades can be a real challenge, but if one follows the full trajectory of the patient's saccades with one's own eye, those saccades are likely to be slow [42]. Moreover, patients with slow saccades often blink or thrust their heads towards the target before making a saccade [43]. Particular attention should also be made to the trajectory of vertical saccades, which are usually curved, not straight, termed the "Round the Houses" sign [44,45]. While supranuclear vertical gaze palsy is considered, amongst other features, to be a distinguishing feature of PSP from MSA or dementia with Lewy body (DLB), it is by itself not diagnostic, and can be occasionally observed, with milder severity than PSP in other degenerative and non-degenerative parkinsonian disorders; an upward gaze palsy can sometimes be seen in normal aged individuals [31,35,46].

Physicians should also look for the presence of square wave jerks (SWJs) when performing eye movement examination in parkinsonian patients. They represent the most common type of saccadic intrusions, characterised by conjugate couplets of back-to-back microsaccades (0.5–5°), which take the eye from the fixation point and back onto it in an involuntary manner under a normal intersaccadic interval of about 200 ms [47]. While SWJs are best observed under Frenzel goggles, large and frequent SWJs can be identified under visual inspection or with an ophthalmoscope. Although SWJs are considered to be nonspecific and frequently observed in patients with neurodegenerative parkinsonisms, cerebellar disorders, or even healthy elderly, certain characters of SWJs may be useful for clinical differentiation of parkinsonism. SWJs are reported to be most common in PSP (60–100%), followed by MSA (40–60%), CBD (33%), and less so in PD (0–15%) [36,48,49]. Different from other parkinsonian disorders, SWJs in PSP are observed to be large (> 5°), frequent (> 16 per minute during fixation or > 20 per minute in the dark), and more markedly horizontal with the latter sign considered to be the most distinguishing feature between PSP and controls [50].

3.2. Nystagmus

Due to the involvement of olivopontocerebellar system in MSA, oculomotor signs can be used to aid diagnosis, including gaze-evoked, downbeat, and rebound nystagmus with impaired smooth pursuit. However, these features are more frequently observed in patients with MSA-C than MSA-P [51,52]. According to the second MSA consensus statement, these oculomotor findings are included as the features for possible MSA-P [2]. The presence of these features can assist physicians in the differentiation between PD and MSA, particularly when other cerebellar signs are not prominent. However, these oculomotor signs were identified in only about one-third of MSA patients based on pathologically proven cases or large longitudinal cohort [52,53]. Therefore, certain techniques can be employed in patients with suspected MSA to induce subclinical nystagmus, including the head-shaking test where patient's head is shaken horizontally in a sinusoidal rate of 2.5 Hz for 10 s and the positioning test where nystagmus is observed following the Dix-Hallpike and straight head-hanging manoeuvres [54]. Using these two tests, perverted head-shaking nystagmus and positional downbeat nystagmus were observed significantly more often in MSA patients compared to PD patients. Together with these features, excessive SWJs (less than PSP but more than PD), moderate saccadic hypometria, and impaired VOR suppression may be considered as red flags for MSA, while the presence of slow saccades and moderate to severe gaze palsy should alert physicians for alternative diagnosis, not MSA [55]. Finally, although limited information is available on eye movement abnormalities in CBD, saccadic apraxia, manifested as increased saccadic latency, is considered as a distinctive oculomotor feature in these patients but observed in only 25% of autopsy confirmed cases [56,57]. In contrast to PSP, saccadic velocities in patients with CBD are usually normal [58].

4. Tremor and jerky limb movements

Tremor-at-rest of a limb is considered as a supportive criterion for a diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) and the Movement Disorder Society (MDS) Clinical Diagnostic Criteria [3,59]. It is also the most visible symptom and frequently the reason why patients request a consultation. The presence of tremor in the setting of parkinsonism can often lead clinicians to consider PD as the most likely diagnosis [5]. Therefore, proper characterisation of tremor or jerks of a limb is essential. Even the absence of tremor at initial presentation has been found to have a diagnostic value in differentiating various types of parkinsonism [60]. In classic parkinsonian tremor, the tremor is manifested primarily at rest with the frequency between 4 and 6 Hz, typically involving the upper limb of the dominant side affected by PD [61]. Its characteristics are often pill-rolling when tremors are limited to fingers, or pronation-supination when progressing to wrist and forearm. This type of tremor may continue to postural conditions. However, there is often an initial pause of up to 10 s, followed by postural tremor of the same frequency (or a difference of no more than 1.5 Hz), often termed as re-emergent tremor [61,62]. Tremor suppression during movement onset in those patients with tremor-at-rest has been identified as the characteristic feature that can separate parkinsonian from essential tremors, and so far, this characteristic has not been observed in APDs [63]. While other types of tremor can also occur in PD, tremor-at-rest is usually evident in the majority of PD patients (65%) at disease onset, with a slightly increased in prevalence during the course of the disease (75%) and is associated with a post-mortem confirmation of the PD diagnosis [64,65].

Although it is generally believed that a lack of tremor as a predominant feature favours the possibility of APDs, a number of clinicopathological or large registry studies have revealed the presence of tremor in a substantial number of patients with APDs [46,60]. However, tremors in APDs are different, providing clues to allow the underlying diagnosis. In general, tremulous movements in patients with APDs are often irregular and more noticeable during ballistic aiming

movements compared to patients with PD [66]. Less frequent than in PD, tremor-at-rest was noted in 39% of pathologically proven MSA cases, with only 8–10% observed to be pill-rolling similar to PD [53,67]. Another large cohort of probable MSA patients revealed that tremor-at-rest was more common in parkinsonism type MSA (MSA-P, 38%) compared to cerebellar type MSA patients (MSA-C, 22%) [52]. However, despite the occurrence of tremor-at-rest in MSA, it is typically not a predominant feature amongst MSA patients [67]. The more common observation amongst MSA patients is the presence of upper extremity, small amplitude 'jerky postural tremor', documented in up to 55% of patients [68,69]. While the clinical term 'jerky postural tremor' can create confusion on the nature of these movements, detailed clinical observation indicates that they are non-rhythmical, involving just one or a few fingers when arms are held outstretched or at the beginning of an action, and rarely involve the whole hand. Further electrophysiological study of these movements showed brief jerks of less than 100 ms, synchronous in antagonist muscles of the forearm, alternating with brief periods of silence, favouring a form of postural and reflex myoclonus (minipolymyoclonus) [68]. This 'minipolymyoclonus' has been included as a supporting feature of MSA under the descriptive term of 'jerky, myoclonic postural/action tremor' in the second consensus statement of MSA [2].

Studies on tremor in PSP are very limited with earlier reports proposing minimal or absent tremor as a diagnostic criterion or supportive feature of PSP [46,70]. However, a recent study documented that half of PSP patients have at least one type of tremor (most commonly postural/action tremor) at some point during their illness, which was usually minimal to mild in severity [71]. The clinical significance of recognising tremors in PSP patients is that their presence is associated with a better response to levodopa compared to patients with PSP without tremor [71]. Tremor-at-rest and action tremors were described in 10–50% of patients with CBD who present with the CBS phenotype although their characteristics were coarse and jerky affecting upper limbs in most cases, and possibly myoclonic and dystonic in nature [72,73]. The myoclonus in CBD is predominantly distal, co-occurring with dystonia in half of cases and are stimulus-sensitive, closely resembling those of cortical reflex myoclonus [73,74].

5. Posture and gait dysfunction

Proper assessments of posture and gait in parkinsonian patients are essential in making a correct diagnosis and treatment planning. Posture and gait dysfunction is also a common cause of disability with a significant impact on disease progression and quality of life [75,76]. Establishing a time course of when these features developed is also an important clue to correct diagnosis as posture and gait abnormalities are usually observed in the early disease stage amongst APDs, but much later in PD. In this section, we have focused on these signs as clinical clues for the differential diagnosis of neurodegenerative parkinsonisms, but the aetiologies are not discussed.

5.1. Postural abnormalities

Camptocormia refers to a pronounced forward flexion of the thoracolumbar spine (usually of at least 45°) during standing or walking, but resolves in a supine position [77]. Amongst various forms of neurodegenerative parkinsonisms, camptocormia is frequently associated with MSA (32.1%) and advanced PD (5.9%) while very few case reports documented its occurrence in patients with DLB [78–82]. Similarly, antecollis, a form of cervical dystonia where there is an excessive fixed forward flexion of the head and neck, is more frequently described in MSA (50%) compared to PD (rare) (Fig. 2A–B) [83]. Prominent features on examination include hypertrophy and active spasms of posterior neck muscles, particularly the splenius capitis and trapezius with occasional anterior neck muscle involvement [84]. In addition, sensory tricks are usually ineffective for this condition. The term 'disproportionate' has been proposed to describe the severity of neck flexion in MSA patients compared to the minor flexed posture of the trunk and limbs [84]. The characteristic 'chin-on-chest' posture with a poor response to levodopa should prompt physicians to consider a possibility of MSA (Fig. 2B) [85]. In addition to its severity, the onset of antecollis in MSA (4.6 years) was found to be earlier than PD patients (10.5 years) [84]. A subgroup of patients with antecollis have also reported a temporal association between the onset of symptom following the use of dopamine agonists [83,86,87]. On the other hand, retrocollis, where the head is held in extension, is highly suggestive of RS although only reported in a minority of patients (Fig. 2C) [88]. Transient head deviation, resembling torticollis, has also been recognised in PSP when forced head deviation occurs in the opposite direction of turning as a result of unopposed vestibulo-collic reflexes [89,90]. Lastly, lateral trunk flexion or Pisa syndrome, defined as lateral trunk flexion $\geq 10^{\circ}$, was identified in 42% of MSA-P patients and only 2.5% of PD patients from the European MSA study group, reaching a specificity of 97.5% (Fig. 2D) [82,91]. Although camptocormia, disproportionate antecollis and Pisa syndrome are overlapped features occurring in both PD and MSA, these features are included as supporting features for MSA, so physicians need to interpret the presence of these features in accordance with the clinical context of individual patients [2].

5.2. Gait abnormalities

Gait disturbances eventually develop in all forms of neurodegenerative parkinsonisms, but the rate of evolution of symptoms, as determined by recurrent falls, can help with differentiation, being shortest in PSP, intermediate in MSA and CBD, and longest in PD [76]. Indeed, recurrent falls within the first year after disease onset can predict PSP in 68–84% of pathologically proven patients [35,76]. Therefore, early detection of gait abnormalities, even subtle, can have both diagnostic and therapeutic implications for affected individuals. Amongst common forms of parkinsonisms described in this review, narrow-based stance is only observed in PD patients, but not PSP and MSA who tend to walk with broad-based (Fig. 3). Asymmetric arm swing, together with ipsilateral hand tremor, has been identified as a supportive feature for PD, not APDs, while broad-based gait, manifested as staggering walk, and en-bloc turning are significantly more common in APDs than PD [92]. All forms of parkinsonisms can be affected by freezing of gait (FOG), but it occurs sooner in APDs, compared to PD, where FOG may also occur as a consequence of motor fluctuations. According to a post-mortem-confirmed APD series, FOG was most frequent in MSA (40%), followed by PSP (25%), and CBD (8%) at a 3-year disease duration, and FOG affects approximately half of PSP and MSA patients three years after [93]. Fall patterns are also different among these patients: PD patients mostly fall forwards due to FOG, but falls in PSP tend to be backwards, associated with more significant injuries than PD [7,94]. 'Drop down' falls are highly suggestive of MSA, usually as a result of orthostatic hypotension.

5.3. Other signs

In addition to the clinical measures discussed above, a patient's ability to perform particular tasks has been evaluated for its diagnostic value in parkinsonisms. Careful observation of decremental effect during finger tapping has been identified as a distinguishing feature between PD and PSP as hypokinesia without decremental response supports the latter diagnosis [95]. The applause sign, characterised by persistent clapping after the patient is instructed to clap three times consecutively as quickly as possible, is seen in up to 70% of PSP patients [96]. It has been attributed to frontal lobe disorder or perseveration. Having said that, the applause sign was found to be highly specific for neurodegenerative parkinsonian disorders (PD, MSA, PSP, and CBD) as well as Huntington's disease, but has no specific role in the differentiation amongst these disorders. A study looking at the ability to perform ten steps with tandem gait in over 80 patients with parkinsonisms whose disease duration was less than 3 years, demonstrated

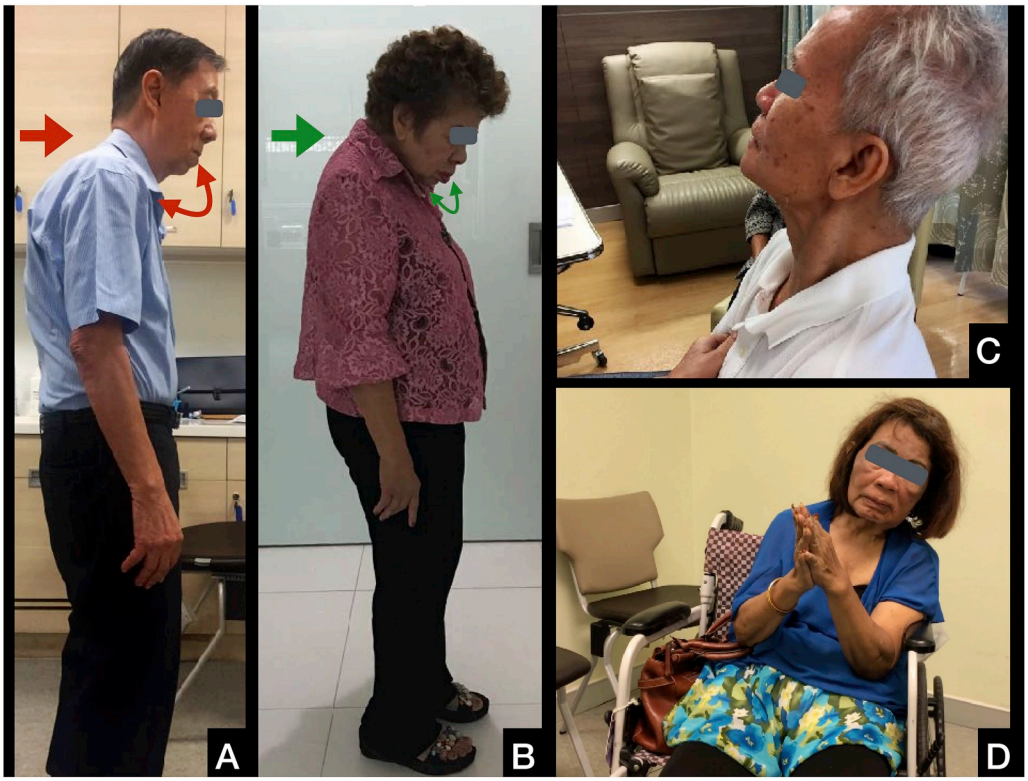

Fig. 2. Posture abnormalities in patients with parkinsonism. 2A: Classic stoop posture in a patient with Parkinson's disease, characterised by mild hip/knee flexion, rounding of both shoulders and mild antecollis; 2B: Characteristic 'chin-on-chest' in a patient with possible multiple system atrophy where there is marked antecollis that is out of proportion of minor flexed posture of the trunk and limbs; 2C: Retrocollis in a patient with Richardson's syndrome; 2D: Lateral flexion of the trunk or pisa syndrome in a patient with probable multiple system atrophy.

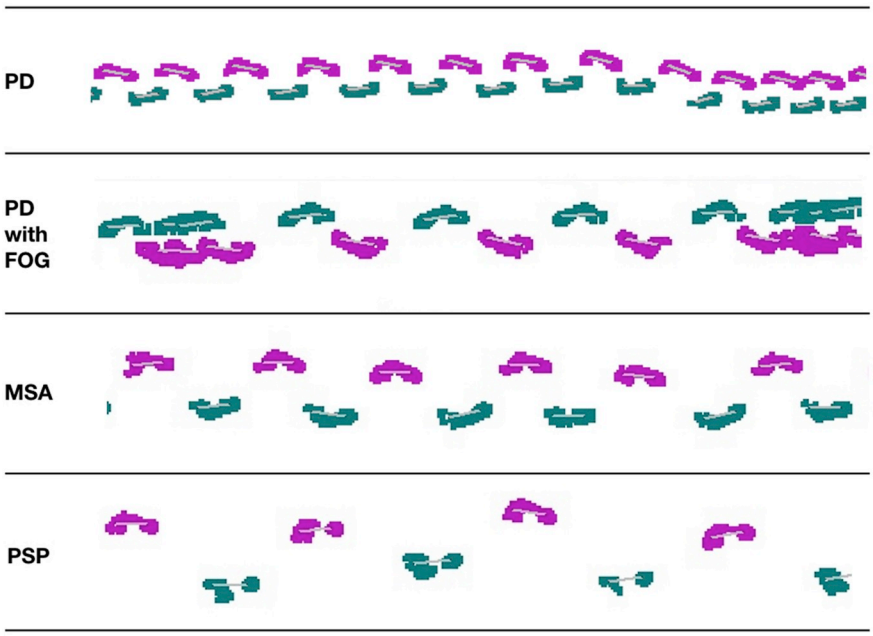

Fig. 3. Footfall patterns in patients with parkinsonism. Top row: typical narrow-based gait pattern in a patient with Parkinson's disease; Second row: Characteristic footfall pattern of freezing of gait in a patient with Parkinson's disease as shown by transient breaks of walking with overlapped steps, frequently observed during gait initiation, turning and termination; Third row: Broad-based gait in a patient with probable multiple system atrophy, reflecting cerebellar dysfunction; Last row: Broad-based gait with increased mediolateral sway in a patient with progressive supranuclear palsy.

that the majority of PD patients (92%) had the ability to perform normal tandem gait without a single side step, where, in contrast, only 18% of APD patients could achieve this [97]. The presence of the bicycle sign, as determined by the loss of cycling abilities after disease onset, has been found to be indicative of APDs (sensitivity and specificity of 52% and 96% respectively) [98]. Lastly, the wheelchair sign, referring to a loss of mobility and the use of wheelchair within the first 3 years, has been proposed as an exclusion criterion for PD [99]. Recently, a number of posture and balance tests have been systematically evaluated for discriminative values between PD and APDs and the highest diagnostic accuracy was achieved using a combination of the tandem gait performance test, retropulsion test, and timed-up-and-go test [100].

6. Conclusion

Differentiating PD from APDs can be a real challenge in clinical practice, particularly in the early stages of the disease. In many cases, diagnosis cannot be ascertained at the initial consultation and clinicians need to incorporate a detailed history with the evolution of clinical signs, supplemented by relevant investigations. Although PD, MSA, PSP, and CBD all share cardinal features of parkinsonism, differences

remain that can be detected by thorough clinical examinations, assisting clinicians in arriving at a proper diagnosis. By following the routine steps of clinical examination, we have outlined clinical clues from four domains, including facial expressions, eye movements, limb tremor/jerky movements and posture/gait, which have been evaluated in the literature to refute or support certain diagnoses (Table 1). However, due to the expanding clinical heterogeneity of degenerative parkinsonian disorders, none of these clinical signs are pathognomonic. Nonetheless, we hope to highlight in this review that even in the era of sophisticated investigations, clinical acumen remains as the central ingredient that individual clinicians must acquire and develop in order to guide their patients and families to the appropriate diagnosis and management of parkinsonian disorders.

Informed consent

Written informed consent has been obtained from all patients to the publication of their photos, in both the printed and online modalities.

Conflicts of interest

The authors have no conflict of interest.

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