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Red flags phenotyping: A systematic review on clinical features in atypical parkinsonian disorders

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ABSTRACT

To establish a clinical diagnosis of a parkinsonian disorder, physicians rely on their ability to identify relevant red flags, in addition to cardinal features, to support or refute their working diagnosis in an individual patient. The term 'red flag', was originally coined in 1989 to define the presence of non-cardinal features that may raise a suspicion of multiple system atrophy (MSA), or at least suggest alternative diagnosis to Parkinson's disease (PD). Since then, the term 'red flag', has been consistently used in the literature to denote the clinical history or signs that may signal to physicians the possibility of an atypical parkinsonian disorder (APD). While most red flags were originally based on expert opinion, many have gained acceptance and are now included in validated clinical diagnostic criteria of PD and APDs. The clinical appreciation of red flags, in conjunction with standard criteria, may result in a more accurate and earlier diagnosis compared to standard criteria alone. However, red flags can be clinical signs that are non-neurological, making the systematic assessment for them a real challenge in clinical practice. Here, we have conducted a systematic review to identify red flags and their clinical evidence in the differential diagnosis of common degenerative parkinsonism, including PD, MSA, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy body (DLB). Increasing awareness and appropriate use of red flags in clinical practice may benefit physicians in the diagnosis and management of their patients with parkinsonism.

1. Introduction

The term 'red flag' was originally proposed by Quinn in 1989 to denote the clinical features in addition to a poor response to levodopa, pyramidal and cerebellar signs that suggested multiple system atrophy (MSA), or at least hinted at an alternative diagnosis to Parkinson's disease (PD) [1]. Since then, the term 'red flag' has been consistently used to refer to clinical features that should cause physicians to reconsider the diagnosis of PD [2]. An increasing number of red flags have been reported with some of them gaining acceptance as part of the standard diagnostic criteria for PD and atypical parkinsonian disorders (APDs) [3–7].

Some red flags relate to particular aspects of clinical history that physicians should obtain during consultation, for example, early falls or rapid progression of gait impairment and balance requiring use of a wheelchair within five years of symptom onset. Other red flags refer to negative findings indicating the absence of certain features expected in PD, such as lack of progression of motor symptoms over five years or a significant response to levodopa, among others [3,8,9]. However, the majority of red flags are clinical signs that require a physician's knowledge and expertise to capture and interpret. Red flags involve different body parts and diverse aspects of the nervous system, often non-motor, and therefore, it is essential to assess systematically [10]. We have adopted the original cartoon of an elephant, proposed by Quinn in 1989, to represent the systematic manifestations of red flags (Fig. 1) [1]. As the diagnosis of parkinsonian disorders primarily relies on relevant history and clinical signs, supported by investigations where necessary, the ability to recognise red flags is an important skill physicians should develop and utilise in their assessment. However, the clinical application of red flags in parkinsonian disorders is limited due to a lack of good sensitivity and specificity of individual features, with the majority of evidence originating from expert opinion, case reports,

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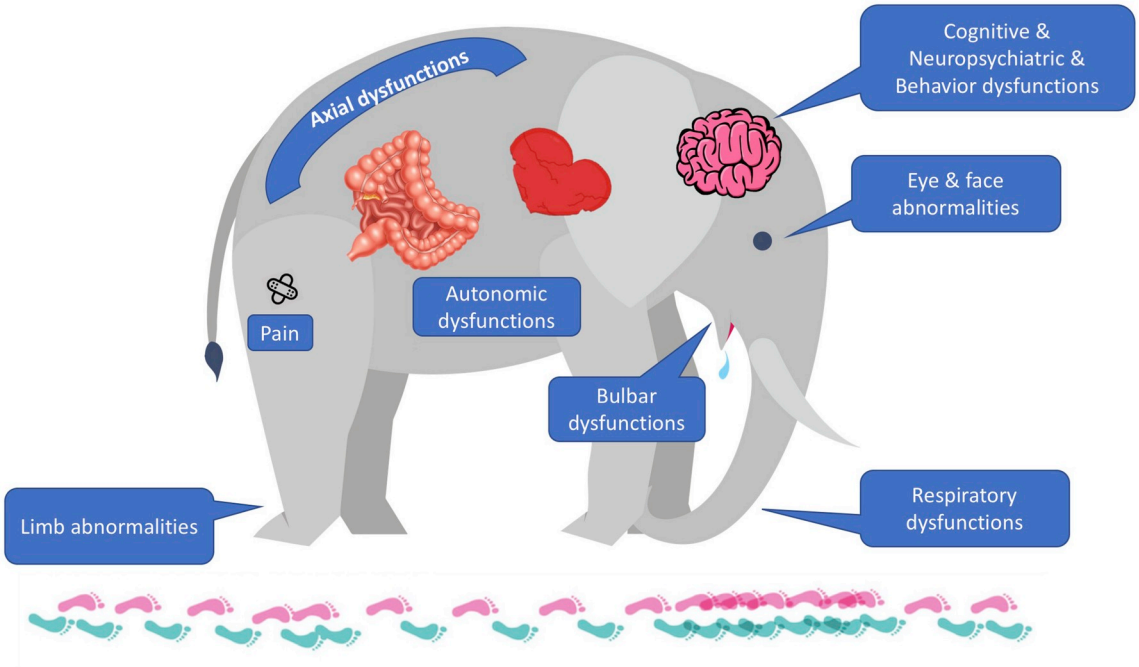

Fig. 1. The illustration of elephant to represent systematic manifestations of red flags. (Adopted from the original cartoon by Quinn 1989 [1]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and case series from a single centre without post-mortem verification of the diagnosis. As specific biomarkers for APDs are not yet available, it is difficult to determine if the atypical features reflect the clinical heterogeneity of APDs, or indicate an alternative diagnosis [11]. Only a few studies have demonstrated the validity of red flags in the diagnosis of APDs, either grouped into related categories or confirmed by post-mortem examinations [12,13]. When applied properly, the identification of red flags can assist physicians to make an early diagnosis. For example, in MSA, an earlier diagnosis of 15.9 months was achieved if red flags and consensus criteria were both applied for diagnosis compared to the consensus criteria alone [12]. A number of atypical features have also been shown to improve the ability to differentiate PD from APDs [14]. Therefore, to aid physicians, we have performed a systematic review of the application of clinical red flags in the differential diagnosis of parkinsonian disorders, including PD, MSA, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Dementia with Lewy body (DLB). Clinical signs of PSP are included within the context of Richardson's syndrome (RS), not other PSP subtypes and the term 'CBD' is used in this review within the context of corticobasal syndrome (CBS) phenotype.

2. Method

A literature search was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines encompassing Ovid MEDLINE, PubMed, EMBASE, Web of Science, Cochrane library, and life science journals to identify articles related to the application of red flags in the diagnosis of PD and APDs [15]. Full search terms and methodology are provided as Supplementary data 1. The definition of 'red flag' was based on the original description by Quinn as stated previously [1]. The search was supplemented with a bibliography of retrieved articles and the authors' knowledge on this subject. Full-text articles published in English between January 1989 and June 2018 relating to the diagnostic use of red flags in PD and APDs were included in this review. As the focus of this review is on clinical red flags, red flags related to investigations (e.g. imaging findings) were not included. Single case reports (except a case with pathological confirmation), editorials, and review articles were excluded. Studies involving subjects without standardised diagnostic confirmation (e.g. validated diagnostic criteria, post-mortem confirmation) and baseline characteristics were also excluded. Case series were included if methods on diagnostic confirmation were clearly presented. Two assessors (RB, JS) independently screened each paper and were required to agree on each study in order for it to be included in this review. We screened 3461 titles and abstracts, from which 267 full-length articles were selected for further review (Fig. 2). Of these, 114 articles fulfilled the selection criteria. Since the feature of each red flag can be either clinical information, which is operationally defined (e.g. rapid progression) or a clinical sign that is based on clinical judgement (e.g. orofacial dystonia, severe dysphonia), all identified red flags were categorised into groups: clinical history or clinical signs (Table 1). The latter was further subdivided into eye/face, limb, axial, and non-motor according to the nature and anatomical involvement of the individual red flag (Table 1).

2.1. Red flags in clinical history

Rapid clinical deterioration despite dopaminergic treatment was mentioned by Quinn as a major red flag for MSA [1]. While the original description lacks any specificity about disease duration, the Movement Disorder Society (MDS) clinical diagnostic criteria for PD has designated *regular* use of a wheelchair within five years of symptom onset as a red flag for an alternative diagnosis [3]. Some studies have defined rapid progression as Hoehn and Yahr stage 3 within 3 years of onset [16]. The term 'wheelchair sign' has been used to denote the early use of a wheelchair observed in patients with APDs, in contrast to patients with PD in whom a wheelchair is used only after many years of disease progression (Fig. 3) [2]. One confounding issue with this red flag is precisely identifying the onset of symptoms, however, most studies identify becoming wheelchair dependent within 5 years of disease onset, as sufficiently distinct from PD to suggest an APD [2,3,12].

The diagnostic accuracy of parkinsonian disorders can also be improved by assessing the time course of the index symptoms of the disease [17]. Early falls, during the first three years, is a common feature of both MSA (60–93%) and PSP (RS) patients (58–88%) [12,18–20]. In contrast, the MDS criteria for PD includes early falls as a red flag, not

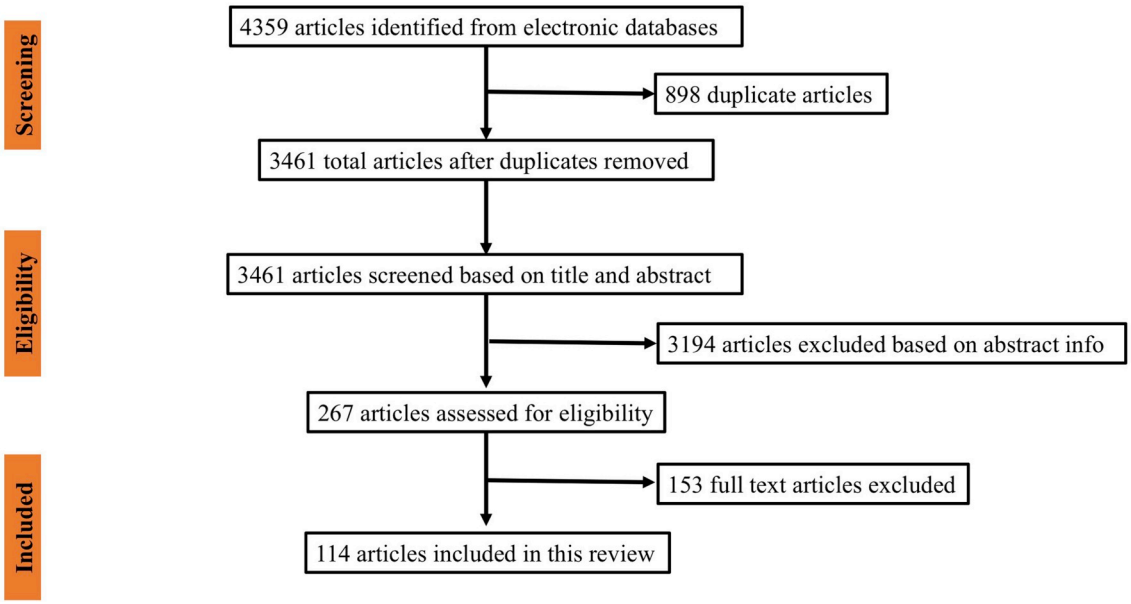

Fig. 2. Diagram illustrating the search results.

keeping with the diagnosis of PD [3,21]. Falls within the first year of disease onset has been shown to predict PSP (RS) in 68–84% of pathologically proven patients [13,22]. The temporal onset of falls, when used to differentiate amongst parkinsonian disorders, was found to be shortest in PSP (6 months), intermediate in MSA, DLB and CBD (24–48 months), and longest in PD (118 months) [22].

A history of hypertension is significantly more common in MSA (about one-third of cases) and PSP (81% of cases) compared to PD [12,23]. While the clinical significance of this finding is unknown, hypertension was also found to precede the first symptoms in MSA patients by several years, but by that time parkinsonian symptoms appear, their blood pressure is usually normo- or hypotensive [1]. It is postulated that the problems in MSA may be related to supine hypertension as the mechanisms behind supine hypertension are likely to be different between PD and MSA with the latter related to cardiovascular autonomic failure [24].

2.2. Red flags of the eyes and face

Several ocular motor and eyelid signs have been identified as red flags for APDs. For example, supranuclear vertical ophthalmoplegia (SVO) is highly suggestive of PSP (RS) and can be occasionally observed, though in milder in severity, in other parkinsonian disorders, including PD dementia, MSA, and DLB [13,20,21,25–29]. However, this sign is not always present during life in pathologically proven cases of PSP, demonstrating that there is an evolution of ocular motor signs and physicians should be able to recognise ocular motor abnormalities that precede SVO. Attention should be focused on proper examination of saccades as pursuit eye movements are disproportionately preserved in PSP patients. When physicians consider the speed, trajectory, and fixation ability of eye movements, different red flags suggestive of PSP can be demonstrated, including slow saccades, curved vertical trajectory of saccades, and large as well as frequent square wave jerks (SWJs) [30–35]. Slow saccades, particularly downward, are considered a hallmark of RS, and are included in both the National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) and MDS clinical diagnostic criteria of PSP [21,25]. 'Messy-tie' sign is a term used to describe the clothes of PSP patients that are soiled with spilled food due to inability to look down at the plate and difficulties swallowing [21]. For degenerative parkinsonian disorders, the presence of slow saccades, especially vertical, strongly favours a diagnosis of PSP and is a very useful red flag for an early diagnosis of PSP, at a time when other clinical signs may not be so prominent [28,30,36,37]. Also, as a result of early vertical gaze centre involvement amongst PSP patients, the vertical trajectory of saccades tends to curve, termed the "Round the houses" sign and this is typically seen before SVO, allowing for an earlier diagnosis of RS [32,34]. SWJs in PSP are observed to be frequent (> 16 per minute), large (> 5°), and more markedly horizontal although SWJs can be present in both MSA and PD and occur as part of normal ageing [33,38].

Ocular motor red flags for MSA-cerebellar type (MSA-C) are related to cerebellar dysfunction, including gaze-evoked, overshoot dysmetria, downbeat, and rebound nystagmus with impaired smooth pursuit [4,39]. An important clinical caveat, though, is that unless specifically look for, ocular motor signs of MSA-C can easily be overlooked as they were identified in only one-third of a large series MSA patients [40,41]. Therefore, physicians may need to bring on subclinical nystagmus by using certain triggers, including head-shaking and positioning tests where positional (head-hanging) downbeat nystagmus can be demonstrated more frequently in MSA than PD patients [42]. Literature on eye movement red flags for CBD is limited with the distinctive feature of increased saccadic latency, termed as saccadic apraxia, identified in only a quarter of CBD patients and this may be mistaken for ophthalmoplegia [43,44]. Although CBD patients are often slow to initiate a saccade, when ultimately done, it is usually of normal range and velocity.

Different forms of facial dystonia have been proposed as red flags for APDs [45]. Dystonic vertical wrinkles in the glabellar region and bridge of the nose, referring to procerus, corrugator, or vertical wrinkling of the forehead sign were reported to be frequent in PSP (40–75%), but rare in MSA (16%) and none in PD [46]. The occurrence of blepharospasm related to the 'off' period may be observed amongst PD patients while its presence in PSP demonstrates no relationship with treatment. Despite variable prevalence (24–70%) of blepharospasm amongst clinical series of PSP, the presence of blepharospasm in pathologically proven PSP cases was found to be low (12.7%) [47–50]. Nevertheless, the diagnostic value of blepharospasm in PSP may increase when it is accompanied by apraxia of eyelid opening such that there is a transient inability to initiate eyelid opening as a result of involuntary levator palpebrae inhibition of supranuclear origin [48,50,51]. In addition, lid retraction, termed 'reptilian stare', though unlikely to be dystonic, is observed in many PSP patients, and along

Table 1
Clinical red flags in atypical parkinsonian disorders classified by clinical history and signs according to topographic involvement.

Atypical parkinsonian disorders	Red flags	
	Clinical history	Clinical signs
MSA	**Rapid clinical deterioration** ● Gait impairment requiring regular use of a wheelchair within 5 years ● Wheelchair dependent within 10 years **Time course of index symptoms** ● Early postural instability and recurrent falls within 3 years	**Eye movement abnormalities** ● Gaze-evoked, downbeat and rebound nystagmus **Abnormal facial appearances** ● Orofacial dystonia **Limb abnormalities** ● Tremulous movements during ballistic aiming movements ● Jerky postural tremor ● Striatal hands ● Contracture of hands and feet **Axial dysfunction** ● Severe dysarthria and dysphagia ● Disproportionate antecollis ● Chin-on-chest posture ● Camptocormia ● Lateral flexion or Pisa syndrome ● Freezing of gait within three years of onset ● A wide-based gait with staggering walk and lateral instability ● Decreased ten-step tandem gait performance ● Loss of cycling ability **Autonomic dysfunction** ● Early severe autonomic dysfunction ● Autonomic dysfunction preceding parkinsonism ● Inspiratory stridor ● Inspiratory sighs, new or increased snoring ● Cold hand signs **Cognitive, neuropsychiatric and behavioural dysfunction** ● Emotional incontinence **Other non-motor symptoms** ● Persistent pain ● Coat hanger pain
PSP	**Rapid clinical deterioration** ● Gait impairment requiring regular use of a wheelchair within 5 years ● Wheelchair dependent within 10 years **Time course of index symptoms** ● Falls within the first year ● Early postural instability and recurrent falls within 3 years	**Eye movement abnormalities** ● Giant or macro square wave jerks ● Curved trajectory vertical saccades (Round-the-house sign) ● Slow vertical saccades ● Supranuclear vertical gaze palsy **Abnormal facial appearances** ● Dystonic wrinkling of the glabellar region (Procerus or corrugator sign) ● Blepharospasm (especially with apraxia of eyelid opening) ● Lid retraction (‘Reptilian stare’) ● A fixed stare with reduced blinking (‘Mona Lisa’ stare) ● Transient head deviation **Limb abnormalities** ● Tremulous movements during ballistic aiming movements **Axial dysfunction** ● Retrocollis with extended body posture ● Freezing of gait within three years of onset ● Robotic voice ● Severe dysarthria and dysphagia within one year of onset ● A wide-based gait with staggering walk and lateral instability ● Decreased ten-step tandem gait performance ● Loss of cycling ability

(*continued on next page*)

Table 1 (*continued*)

Atypical parkinsonian disorders	Red flags	
	Clinical history	Clinical signs
		Cognitive, neuropsychiatric and behavioural dysfunction ● Executive dysfunction and apathy within three years of onset ● Apathy and impulsivity (Rocket's sign) ● Emotional incontinence ● Non-fluent aphasia **Other non-motor symptoms** ● Decreased pain sensitivity ● Absent of autonomic symptoms
CBD	**Rapid clinical deterioration** ● Gait impairment requiring regular use of a wheelchair within 5 years ● Wheelchair dependent within 10 years	**Eye movement abnormalities** ● Saccadic apraxia **Limb abnormalities** ● Jerky dystonic movements (especially when asymmetric) ● Useless arm ● Alien limb phenomenon ● Limb levitation ● Contracture of hands and feet ● Dystonic clenched fist ● Tremulous movements during ballistic aiming movements **Axial dysfunction** ● Severe dysarthria and dysphagia within one year of onset ● A wide-based gait with staggering walk and lateral instability ● Decreased ten-step tandem gait performance ● Loss of cycling ability **Cognitive, neuropsychiatric and behavioural dysfunction** ● Ideomotor apraxia ● Non-fluent aphasia
DLB	**Rapid clinical deterioration** ● Gait impairment requiring regular use of a wheelchair within 5 years ● Wheelchair dependent within 10 years ● Parkinsonism (typically symmetrical without tremor) poorly responsive to levodopa	**Limb abnormalities** ● Tremulous movements during ballistic aiming movements **Axial dysfunction** ● Severe dysarthria and dysphagia within one year of onset ● Decreased ten-step tandem gait performance ● Loss of cycling ability **Cognitive, neuropsychiatric and behavioural dysfunction** ● Early dementia (within one year of the appearance of parkinsonism) ● Fluctuating cognition ● Early and prominent visual hallucinations

APD: Atypical parkinsonian disorder; MSA: Multiple system atrophy; PSP: Progressive supranuclear palsy; CBS: Corticobasal syndrome.

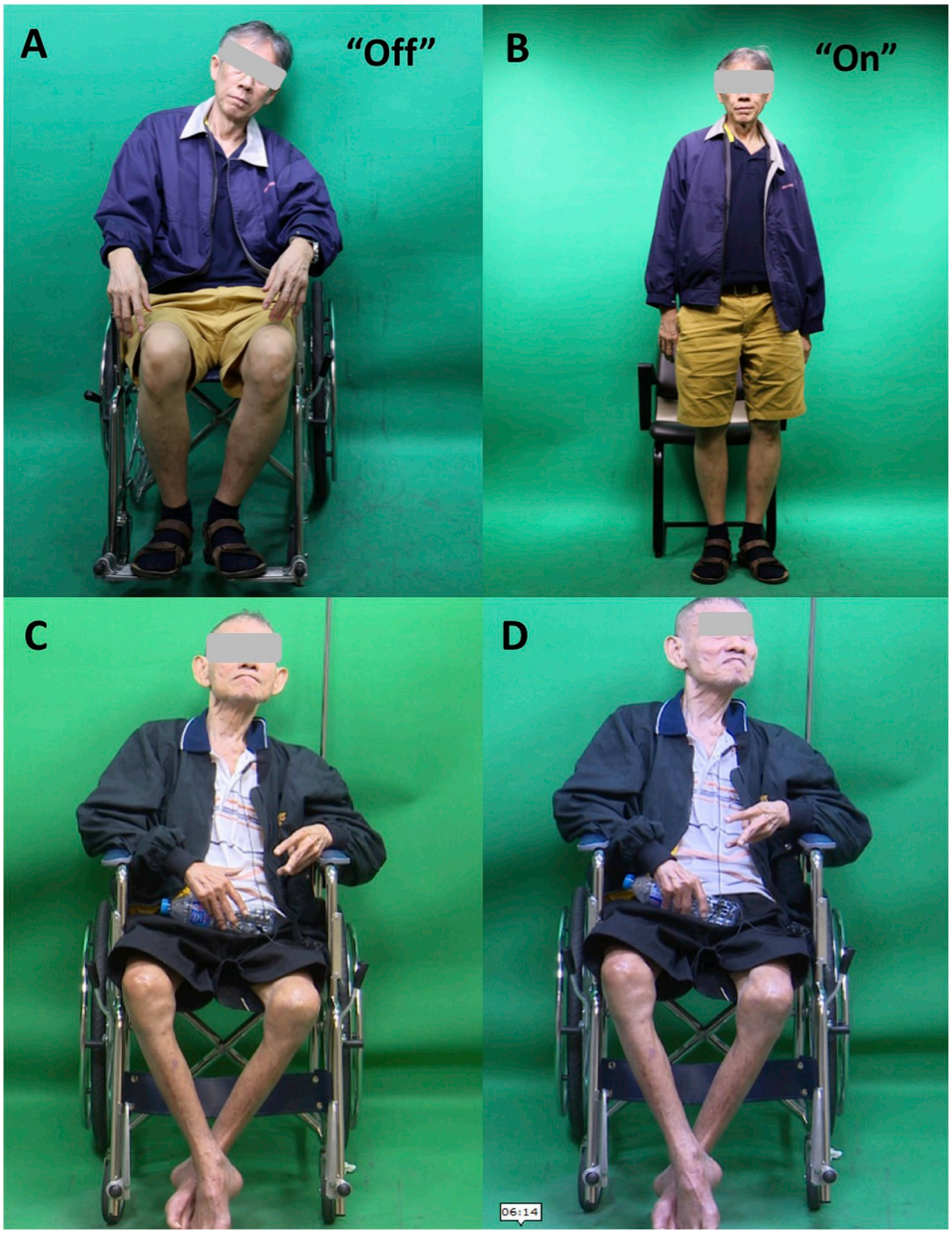

Fig. 3. Intermittent use of wheelchair in Parkinson's disease patients during the 'off' period (3A-B). This is in contrast to persistent use of wheelchair by a patient with atypical parkinsonian disorder (3C-D).

with deepened facial lines results in an anguished, astonished or worried expression [51]. In its full-blown form, PSP patients may exhibit a fixed "Mona Lisa" stare, associated with a markedly reduced blink frequency [21]. Transient head deviation, mimicking torticollis, is another feature recognised amongst PSP patients, when forced head deviation occurs in the opposite direction of turning as a result of unopposed vertibulo-collic reflexes [52,53]. Dystonia of the lower face (orofacial dystonia) is a well recognised red flag for both PSP and MSA, frequently observed following a dopaminergic administration, whereas a 'risus sardonicus'-like appearance has been described amongst MSA patients [4,54,55].

2.3. Red flags of the limbs

In contrast to PD, tremor-at-rest in PD is very uncommon in APDs and in the latter, tremulous movements are usually irregular, stimulus-sensitive, and more noticeable during ballistic aiming movements [56]. When arms are held outstretched or at the beginning of an action, 'jerky postural tremor' or 'minipolymyoclonus' may be observed in approximately half of MSA patients, and is characterised by non-rhythmical movements of a few fingers that can be stimulus-sensitive representing a form of reflex myoclonus [4,57,58]. In CBD with corticobasal syndrome (CBS) phenotype, jerky movements are reported as predominantly distal and coarse, co-occurring with fixed dystonia in half of cases and frequently stimulus-sensitive [59,60]. However, this classic presentation has also been reported in patients with Alzheimer's pathology [61,62]. The term 'useless arm' has been described in 30% of CBS patients to denote an 'alien' arm that wanders and grasps (without release) onto parts of the body, bedclothes, adjacent furniture or, less likely, people, interfering with normal tasks [5,63]. The presence of the alien limb phenomena is included as a feature, supporting the diagnosis of probable and possible CBS and must be differentiated from simple limb levitation, which may also occur in PSP and other parkinsonian disorders [5,64].

Contracture of hands and feet is included as a red flag supporting the diagnosis of MSA, characterised by a striatal hand formed by flexion

of the metacarpophalangeal joints, flexion of the distal interphalangeal joint, flexion of the distal interphalangeal joints, and ulnar hand deviation, and associated with pain [4,65]. However, this feature is not exclusive to MSA as it is also described less commonly in other parkinsonian disorders, including advanced PD, PSP, and CBD [1,12,40,47,66–68]. Overall, the presence of limb contractures has been shown to associate with higher disease severity, levodopa usage, and the side of initial parkinsonian symptoms [69]. Where different forms of contractures, not limited to striatal deformities, have been described in the literature, the appearance of limb contractures is likely to develop as a result of a long-standing fixed dystonia [70]. For example, with 'dystonic clenched fist' the hand is held in a flexed, typically fixed dystonic posture with clenching of fingers into a fist, closing around the thumb, adducted in the palm [71].

2.4. Axial red flags

Although dysarthria and dysphagia occur in all forms of parkinsonism, including PD, it is their timing and severity which make them potential red flags. Severe dysphonia and dysarthria, in the context of short disease duration, have been indicated as signs supporting the diagnosis of MSA [4]. The temporal evolution of dysarthria and dysphagia has been studied in pathologically confirmed cases of parkinsonian disorders, indicating a very high specificity for APDs if either feature occurs within one year of onset [72]. Dysarthria was also found to occur earlier than dysphagia in all forms of parkinsonian disorders, including PD. While both features occur as late complications in PD, they occur very early in PSP, within 24 and 42 months for dysarthria and dysphagia respectively [72]. In MSA, there is an early onset of dysarthria that is similar to PSP, but the appearance of dysphagia occurs much later, at 67 months. Early dysarthria in MSA reflects the presence of either vocal cord paralysis or laryngeal dystonia even in the early disease stage, producing a strained-strangled voice with pitch and intensity variations that may be diagnostic by itself in certain patients [1,73]. When examined under laryngoscopy, upper airway obstruction in places other than the vocal cords have been identified, including the base of the tongue and soft palate [74]. On the other hand, dysarthria in PSP is dominated by dysfluency with hypokinetic and spastic components, interrupted by multiple silences and has a 'robotic' quality to it [73,75].

Different forms of head and neck posture have been described in parkinsonian patients as potential red flags. Antecollis, characterised by forward flexion of the head and neck, has been found to be more common in MSA (36.8%) than PD (0.8%) [12]. In addition, antecollis in MSA is described as being disproportionate, with a discrepancy between severe neck flexion and minor flexed posture of the trunk and limbs, termed as 'chin-on-chest' posture [76,77]. However, this phenomenon is not an absolute discriminator between MSA and PD, and the determination of 'disproportionate' is often subjective. In contrast, the presence of retrocollis, where the head is held in extension, together with extended body posture, is highly suggestive of RS, although only reported in a minority of patients [78,79]. Abnormal trunk posture has been defined by several terms, depending on the plane of deviation. When sagittal displacement is observed, the term 'camptocormia' has been used to indicate a pronounced forward flexion of the thoracolumbar spine during standing or walking that resolves in a supine position [80]. Marked coronal displacement of the trunk is described as lateral flexion or Pisa syndrome [81]. With the exception of retrocollis, all the above-mentioned features are included as supportive red flags for MSA, and found to have a specificity of above 90% when compared to PD from the European MSA study group [12].

Visual inspection of gait patterns can elicit potential red flags for differentiating PD from APDs. Asymmetric arm swing, together with ipsilateral hand tremor, is very indicative of PD, but not APDs [82]. A wide-based gait when accompanied by staggering walk with lateral instability is very indicative of APDs [82]. While freezing of gait (FOG) is a shared feature amongst degenerative parkinsonisms, its timing makes it a potential red flag; in PD, FOG occurs in the middle or latter stages whereas early FOG suggests an APD. In a post-mortem case series, early FOG was as frequent in both MSA (40%) and PSP (25%), but rare in CBD (8%) [83]. Indeed, FOG has been identified as a presenting symptom in 18% of possible PSP patients before the NINDS-SPSP criteria was fulfilled, however, pathological verification of these cases was lacking [84].

A patient's ability to perform particular gait and mobility tasks has also been identified as potential red flags for APDs. When ten steps performance on tandem gait was evaluated in APD patients, only 18% of patients could achieve this compared to 92% of PD patients with the same disease duration of less than 3 years [85]. Similarly, the loss of cycling ability after disease onset has been found to be indicative of APDs with a sensitivity and specificity of 52% and 96% respectively [86]. Recently, a combination of clinical tests, including tandem gait performance, retropulsion, and time-up-and-go, have been identified as having good discriminative value between PD and APDs [87].

2.5. Non-motor red flags

2.5.1. Red flags on autonomic dysfunction

Autonomic failure (AF) is a common non-motor feature in synucleinopathies (PD, MSA, DLB), but the presence of AF alone does not *per se* aid in the clinical differentiation between these disorders [88,89]. However, the assessment of AF usually relies on the presence of orthostatic hypotension, which has been found to be an insufficient clinical sign for differentiating amongst parkinsonian disorders, particularly MSA and PD [90]. Nevertheless, for diagnostic purposes, physicians should be aware of certain clinical features or patterns of AF, which could be used as red flags. In comparative studies of pathologically confirmed MSA and PD or PSP, the presence of severe AF and its onset preceding motor signs of parkinsonism have been identified as features suggesting MSA [91,92]. In MSA, the presence of symptomatic orthostatic hypotension frequently occurs after the onset of erectile dysfunction and urinary incontinence [4,93–95]. Once orthostatic hypotension is established, it is essential to evaluate patients for the presence of nocturnal hypertension, although this feature alone probably has no definite diagnostic value as it is documented in at least 40% of patients with PD, MSA, and PSP [96]. Prominent AF should not be observed in patients with PSP, making it a non-supportive red flag for this disorder [97].

Various respiratory dysfunctions are observed in patients with APDs with some proposed as supportive red flags. Inspiratory stridor, as a result of laryngeal abductor spasm or vocal cord dystonia, has been identified as a suggestive feature in MSA, commonly observed in up to 69% of patients [40,91,98]. Its presence during the daytime carries a poor prognosis, identified as a cause of sudden death in MSA patients [99]. Although less studied, inspiratory sighs and new or increased snoring are commonly observed amongst MSA patients in clinical practice, and are included as supportive features for MSA in the second consensus statement [4,100]. As a result of neurovascular control defect of distal extremities, cold, dusky, violaceous hands can be observed in some patients with MSA, representing another red flag, as hand skin temperature was found to be lower in MSA than PD patients [101,102].

2.5.2. Red flags on cognitive, neuropsychiatric and behavioural dysfunction

Recent evidence supports the presence of cognitive, neuropsychiatric and behavioural dysfunction of at least mild severity in the early stages of all forms of degenerative parkinsonian disorders [103,104]. Therefore, their presence alone cannot be used as a distinguishing feature amongst degenerative parkinsonian disorders. However, similar to AD, certain features or patterns of cognitive, neuropsychiatric and behavioural dysfunction have been proposed as red flags. The presence of severe cognitive impairment or profound dementia early in the disease course should raise the suspicion of PSP and DLB where cognitive

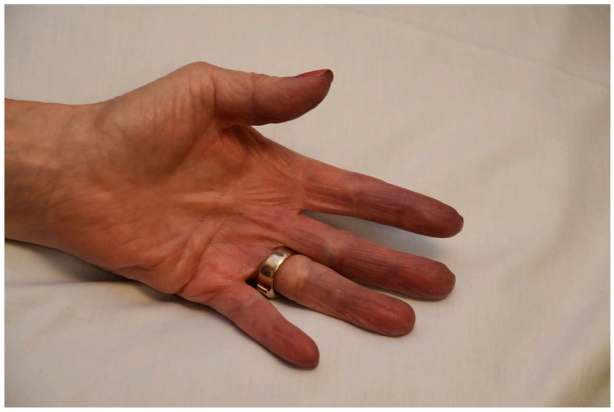

Fig. 4. Cold hand sign in a patient with multiple system atrophy.

dysfunction represents one of the core criteria for the diagnosis of these two disorders [6,21]. Based on a single study involving 181 parkinsonian patients, visual hallucinations were identified as a red flag to discriminate between PD and APDs, but DLB were not represented in this cohort [105]. However, when compared to PD in another post-mortem study, the presence of hallucinations in the absence of gait or balance dysfunctions were identified as clinical pointers for DLB [106]. While 40–75% of PD patients were screened by Queen Square Visual Hallucination Inventory to have visual hallucinations, none of MSA patients and only 14% of PSP patients reported minor hallucinations. Moreover, isolated auditory hallucinations were only observed in PD patients, but not in APDs. Indeed, the presence of visual hallucinations is proposed as a non-supportive red flag (exclusion criteria) for PSP-parkinsonism [107]. Parkinsonian patients with fluctuating cognition with pronounced variations in attention and alertness, manifested as daytime drowsiness, staring into space and incoherent speech, without other obvious causes should raise the suspicion of DLB [6]. These features can also discriminate between DLB and Alzheimer's disease [108,109].

Preferential involvement of cognitive domains should be identified in parkinsonian patients as certain prominent features may pose as red flags. Deficits in frontal function, manifested as executive dysfunction and apathy, are highly suggestive of PSP, affecting up to three quarters of patients [110,111]. The applause's sign, characterised by persistent clapping after the patient is instructed to clap three times consecutively as quickly as possible, was initially observed in up to 70% of PSP patients, but was later identified with probably less frequency in other forms of parkinsonian disorders, including PD, and cortical dementias [112–115]. Even in the presence of apathy, PSP patients may exhibit impulsivity, observed by carers as motor recklessness, predisposing those with prominent axial disability to fall-related injuries [10,116]. The term ‘Rocket sign’ has been used to describe a particular feature of motor recklessness when PSP patients may jump to his or her feet from a sitting position without thinking only to topple backwards into the chair because of postural instability [117]. Indeed, prominent ‘frontal’ cognitive deficits within the first 3 years have been identified as a predictor of PSP compared to PD [13,118]. Emotional incontinence, described as inappropriate crying, or less frequently, laughing in the absence of sadness or mirth, is a red flag for PSP and MSA as it is observed in approximately one-third of MSA and PSP patients, but rare amongst PD patients [12,119,120]. In CBD, visuospatial deficits, frequently manifested as ideomotor apraxia, seem to be a distinctive feature compared to MSA and PSP patients [121,122]. While memory tends to be preserved in most cases of CBD in the early stage, limb apraxia frequently occurs in association with executive dysfunction and worsening language performance, of which apraxia of speech and non-fluent aphasia are suggested as red flags for both CBD and PSP [123,124].

2.5.3. Other non-motor red flags

While pain is recognised as a common non-motor feature in both MSA and PD patients, its character may be considered as a red flag for MSA; pain in MSA is usually experienced as deep aching limb pains that occurs throughout the day that is not relieved by levodopa [1,89,125]. Moreover, compared to healthy subjects, reduced sensitivity to heat has been observed amongst MSA patients, posing an important consideration for carers when applying warm blanket to cold hands and feet in affected individuals (Fig. 4) [126]. Coat hanger pain is peculiar neck pain radiating to the occiput and shoulders, reported in 53% of MSA patients with orthostatic hypotension [127]. It typically worsens in the morning, with warm temperatures, while standing, during straining and post-prandially, while it is relieved by lying flat. In contrast, pain was reported significantly less in PSP compared to MSA and PD patients [125,128].

3. Conclusion

When confronted with a patient with parkinsonism, the first question is whether it is PD or another cause of parkinsonism. The distinction is largely based on identifying signs that are typical for PD versus those that are atypical, a ‘red flag’, suggesting an APD, such as MSA, PSP, CBD, or DLB. In this systematic review, we have provided a detailed list of red flags that may be identified in a pertinent clinical history, or are clinical signs including: cardinal features of parkinsonism; various types of abnormal movements; neurological signs that are unrelated to movement disorders; or non-neurological signs that can be observed as part of a comprehensive assessment, providing the rationale evidence for physicians to utilise these red flags in their clinical practice. Recognition of multiple red flags in an individual patient may increase the likelihood of APD and while the initial identification of red flags mainly originated from expert opinion, many of them have gained stronger evidence in the form of clinicopathological, multi-centre, or clinical studies with several now incorporated into recent clinical diagnostic criteria for parkinsonian disorders [3–5,21]. In some clinical situations, the manifestation of certain red flags may be so distinct that physicians may rely on it in making a diagnosis. However, we recommend that physicians follow a step-wise approach in the diagnostic work-up of parkinsonism, by first establishing parkinsonian features, though they may be mild or subtle in some situations, before searching systematically for red flags. None of the red flags identified in our systematic review is clinically pathognomonic, and, though, a few may be relatively distinctive, the majority can be observed in a number of conditions. Moreover, certain red flags are observed uncommonly in common disorders, while some may be commonly identified in uncommon disorders. Therefore, though these flags can be a helpful aid, ultimately it is for physicians to make a balanced judgment when making a clinical diagnosis in an individual patient.

Conflicts of interest

The authors have no conflict of interest.

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Appendix A. Supplementary data

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