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Review article

Dystonia in atypical parkinsonian disorders

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ABSTRACT

Dystonia is common in the classic atypical parkinsonian disorders such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration, and to a lesser extent in dementia with Lewy bodies. Its clinical phenomenology, including body distribution, timing of appearance, severity, and relationship to dopaminergic and other medications may vary considerably within and between atypical parkinsonian disorders. From a pathophysiological standpoint, the coexistence of dystonia with parkinsonism challenges the functional model of the basal ganglia. Clinical recognition of specific dystonic features may assist in the differential diagnosis of atypical parkinsonian disorders and in distinguishing them from Parkinson's disease. The presence of dystonia in atypical parkinsonian disorders informs management decisions. Reduction or withdrawal of levodopa should be considered if there is a close relationship between the onset of dystonia with periods of high dopaminergic tone. Botulinum neurotoxin may be considered in focal presentations. We here provide an updated overview of dystonia arising in the setting of atypical parkinsonian disorders, summarizing relevant clinical and clinicopathological studies, underlying pathophysiological mechanisms, diagnostic clues and potential pitfalls in the diagnosis. Finally, we suggest a tailored therapeutic approach for the management of these patients.

1. Introduction

The term atypical parkinsonian disorders (APD) applies collectively to Parkinson's disease (PD)-like neurodegenerative diseases, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB). APD are primarily characterized by the combination of parkinsonism with additional motor and non-motor features that are beyond the spectrum of PD.

Over the past few decades, dystonic features in APD have been better characterized, with disease-specific differences noted in prevalence, body distribution, severity, timing in respect to the onset of parkinsonian features, and relationship with dopaminergic treatment [1]. In some instances, the temporal and topographical distribution of dystonia in APD may assist in reaching a “clinically probable” diagnosis of APD (e.g., laryngeal dystonia or Pisa syndrome in MSA and limb dystonia in CBD within the classical presentation of corticobasal syndrome - CBS) [2–4] (Fig. 1). However, there are notable discrepancies between studies reporting clinical prevalence and characteristics of dystonia in APD, which may be explained by methodological factors, such as limited number of patients, single-center design, or lack of pathologic confirmation [5]. Hence, the prevalence of dystonia and the extent to which the different dystonic manifestations are specific for different APD have not been fully elucidated. Another largely unexplored issue concerns the pathophysiology of dystonia in APD [6]. Greater understanding of the phenomenology and pathophysiology of dystonia in APD are relevant for improved diagnostic and therapeutic approaches.

We here review clinical and clinicopathological studies on dystonia in APD organized using a rostro-caudal topographical criterion. We discuss the pathophysiology of dystonia in APD in connection with the associated degeneration in the basal ganglia and connected structures,

Abbreviations: APD, atypical parkinsonian disorders; BoNT, botulinum neurotoxin; CBD, corticobasal degeneration; CBS, corticobasal syndrome; DBS, deep brain stimulation; DLB, dementia with Lewy bodies; M1, primary motor cortex; MSA, multiple system atrophy; MSA-P, MSA-parkinsonian subtype; MSA-C, MSA-cerebellar subtype; PD, Parkinson's disease; PSP, progressive supranuclear palsy; PSP-R, progressive supranuclear palsy-Richardson's syndrome variant

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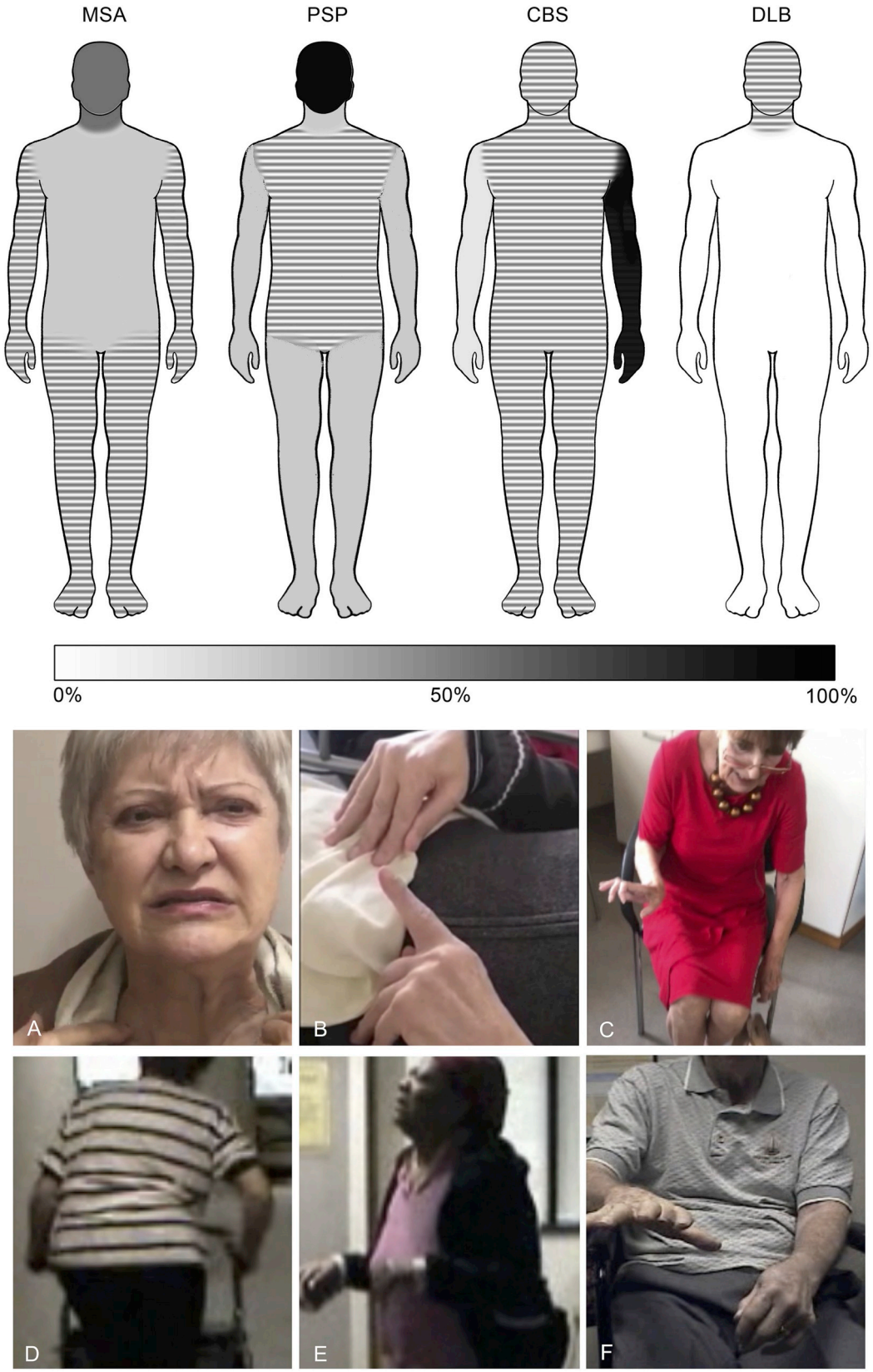

Fig. 1. Body distribution, prevalence, and selected dystonia phenotypes in atypical parkinsonian disorders. Upper panel: **MSA**: orofacial and craniocervical dystonia: 16–67%; anterocollis: 2–42%; laryngeal dystonia (including stridor): 0.7–49%; limb dystonia: 0.7–53%; trunk dystonia, manifested as Pisa syndrome: 42%, and camptocormia: 5–32%. **PSP**: blepharospasm: 10–100%; other craniofacial/oromandibular dystonias: 2–29%; cervical dystonia (retrocollis): 17–25%; and limb dystonia: 5–26%. **CBS**: limb dystonia: 14–100%; rare forms of dystonia as blepharospasm, cervical dystonia (retrocollis), and levodopa-induced lower limb dystonia have been reported. Horizontal lines indicate anecdotal involvement but no known prevalence estimates. Lower panel: Orofacial dyskinesia (A) and Pisa syndrome (D) in MSA; "Pointing gun" posture (B) and retrocollis (E) in PSP; marked asymmetric limb dystonia in CBS (C, F).

highlight the experimental studies offering clues on the functional reorganization of brain networks underlying dystonia in APD, and address clinical issues that may be useful in the differential diagnosis among APD and between APD and PD, including dystonia mimics and special cases. Finally, we summarize the pharmacological and non-pharmacological approaches for the management of dystonia in APD and propose steps for future research.

Search strategy: PubMed was searched for full-text papers (original studies and reviews) published in English by December 2018. The search terms used were "dystonia", "atypical parkinsonian disorders" "atypical parkinsonisms", "multiple system atrophy", "progressive supranuclear palsy", "corticobasal degeneration", "corticobasal syndrome" and "dementia with Lewy bodies" in isolation and in combination. Relevant papers were also selected from the reference lists of identified articles. Rare genetic causes of dystonia and parkinsonism were excluded.

2. Epidemiology and clinical phenomenology

2.1. Dystonia in multiple system atrophy

While dystonia was considered a rare occurrence in MSA prior to 1990 [7], more recent reports suggest the prevalence of dystonia in MSA might not be low (Table 1).

Cranial dystonia, particularly orofacial dystonia, is a common manifestation in MSA patients. It consists of tonic spasms of the lower face and lips, conveying an expression that resembles the tetanic "*risus sardonicus*" [8,9] (Fig. 1, lower panel: A). It particularly occurs in the parkinsonian subtype (MSA-P) approximately 2–3 years after treatment initiation with levodopa, with an estimated prevalence ranging from 16% to 67% of cases [5,10–12].

Cervical dystonia in MSA, commonly MSA-P, manifests as anterocollis, marked forward neck flexion greater than 45° resulting from involuntary muscle contraction, with an estimated prevalence ranging from 2% to 58%, affecting both drug naïve and dopaminergic medication-treated patients [5,10,11,13,14].

Respiratory stridor, either diurnal or nocturnal, is a dystonic manifestation affecting the vocal cords whereby a nickering sound with a pitch higher than that of ordinary snoring (around 260–330 Hz) is produced by air passing through a narrowing in the vocal cords during inspiration. Respiratory stridor in MSA has an estimated prevalence ranging from 15% to 37% [11,15–17], with a slightly higher prevalence in the MSA-P subtype [18]. Among MSA-P patients, nocturnal inspiratory stridor is more common (37.7%) than diurnal inspiratory stridor (22.8%) [11]. Respiratory stridor clusters in a more malignant subtype of MSA.

Trunk dystonia expresses as lateral deviation (Pisa syndrome) or forward posturing (camptocormia), in both cases resolving or substantially improving in the supine position [19–22]. Originally considered to resemble an acute dystonic reaction from neuroleptic exposure [23], axial dystonia is recognized as a relatively common feature of in MSA [24]. Pisa syndrome has been reported in 42% of patients with probable and possible MSA-P and is now considered one of the most important "red flags" (e.g., warning signs) favoring a diagnosis of MSA [11] (Fig. 1, lower panel: D). Camptocormia has been documented to occur from 22% up to 26% in MSA-P [11,13].

Limb dystonia (mainly unilateral), in the more affected hand or foot (including the "striatal toe", an abnormal extensor posturing of the big toe in the absence of cortico-spinal tract involvement) [25] has been reported in up to 0.7–53% of MSA patients [7,10,15].

2.2. Dystonia in progressive supranuclear palsy

Dystonia has been recognized as a common manifestation of the classical PSP phenotype since the original descriptions of the disease [26,27] (Table 2).

Cranial dystonia, particularly *blepharospasm*, consisting of intermittent or persistent involuntary closure of the eyelids, is a common dystonic feature in PSP, reported on average in ~40% of cases, with variable percentages ranging from 10 to 100% of cases [28–34]. *Apraxia of eyelid opening* is considered a variant, or earlier form, of blepharospasm in half of PSP patients, and corresponds to an isolated contraction of the pretarsal component of the *orbicularis oculi* muscle [35,36]. The inability to voluntarily open or close the eyes cannot be explained by focal muscle weakness or deficits in the third or seventh cranial nerves [30,33,34].

Other features of facial dystonia in PSP include deepening of nasolabial folds, the *procerus sign* (contraction of the *frontalis*, *procerus* and *corrugator* muscles) [37,38], and the "reptilian stare" (astonished facial expression), from widening of the palpebral fissures due to frontalis muscle overactivity [4,9,38]. There is a high prevalence of facial dystonias in PSP, reaching up to 29% of cases [5]. Levodopa-induced oromandibular dystonias have been reported in PSP cases [12,39–41] but these are distinctly unusual.

Cervical dystonia in PSP characteristically manifests as retrocollis, i.e. abnormal head hyperextension, occurring in 17–25% of cases [12,33] (Fig. 1, lower panel: E), although occasional patients can exhibit anterocollis, similar to MSA and PD [13]. In the classic variant of PSP, the Richardson's syndrome (PSP-R), retrocollis is related to axial rigidity and is associated with recurring cervical pain [33]. The retrocollis of PSP is not usually associated with other dystonic neck movements or muscle hypertrophy and is not modified by the "*geste antagoniste*". Therefore, it is debatable whether retrocollis represents a true dystonic manifestation. Alternative terms have been proposed, for example "nuchal rigidity in extension", which more closely resembles the original description by Steele and colleagues of "nuchal dystonia" [26,33].

Limb dystonia, including the peculiar "pointing gun posture" (e.g., extended thumb and index finger together with flexion of the other fingers) has been described in up to 26% of PSP cases [7,13,33,42–44], but tends to occur in late stages [44] (Fig. 1, lower panel: B). Hemidystonia may present early in 11% of PSP cases, even before the onset of the typical oculomotor abnormalities, suggesting a clinical diagnosis of CBS [33].

2.3. Dystonia in corticobasal syndrome

Unilateral arm dystonia is a cardinal feature of CBS [2], occurring in the majority of cases (ranging from 14 to 100%, according to the different studies) and characterized by adduction and flexion of the affected arm, forearm, wrist and metacarpophalangeal joints, and extension of the interphalangeal joints [45–47] (Fig. 1, lower panel: C, F). The literature, however, must be parsed out for the differences in reports of clinically diagnosed CBS (26–56% of whom had CBD and 7% PSP pathology) versus pathologically proven CBD cases (37% of whom had CBS and 23% PSP syndrome) [2,44,48] (Table 3). Among a large series of pathology-proven CBD published from 1968 to 2012, upper limb dystonia (n = 404, 374 with available data) was identified in ~17% of cases [48]. In CBS, arm dystonia occurs early and without fluctuations, and may progress to involve the ipsilateral leg.

Rare dystonic manifestations in CBS include blepharospasm, cervical dystonia (both anterocollis and retrocollis) [45,49], and levodopa-induced lower limb dystonia, characterized by internal rotation and flexion of the hip, flexion of the knee and inversion of the foot [12,45,49], usually reversed by medication reduction or withdrawal [50–52].

2.4. Dystonia in dementia with Lewy bodies

To date, no systematic study on the prevalence of dystonia in DLB is available. Single case reports and case series are the only source of information. Segmental cranial dystonia characterized by the combination of oromandibular dystonia and blepharospasm, is the most

Table 1
Frequency and distribution of different types of dystonia in MSA.

Dystonia Type	Dystonia Frequency	Disease Subtype	Study Type	Pathologic confirmation (n° patients)	Author(s)
Facial dyskinesia/dystonia	(67%) 20*/35	OPCA/SND	Retrospective chart review	35	[16] Wenning et al., 1995
	(42%) 5*/12	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
	(25%)17/67	MSA-P	Cross-sectional (Follow-up in 17)	NA	[11] Kollensperger et al., 2008
	(25%) 25*/100	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
	(16%) 31/191 (3*/31)	MSA	Prospective, 5 y follow-up	NA	[5] Yoon, 2018
Cervical NS	(58%) 7*/12	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
	(25%) 6/24	MSA-P/MSA-C	Prospective follow-up	5	[10] Boesch et al., 2002
	(2%) 5/191 (1*/5)	MSA	Prospective follow-up	NA	[5] Yoon, 2018
Anterocollis	(42%) 8/19	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
	(37%) 25/67	MSA-P	Cross-sectional (Follow-up in 17)	NA	[11] Kollensperger et al., 2008
	(8%) 2/23	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(9%) 9/100	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
	(2%) 3/140	OPCA/SND	Literature review	140	[7] Rivest et al., 1990
Retrocollis	(4%) 1/23	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(53%) 53*/100	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
	(25%) 3*/12	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
	(26%) 5/19	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Limb dyskinesia/dystonia	(20%) 5/24	MSA-P/MSA-C	Prospective follow-up	5	[10] Boesch et al., 2002
	(15%) 10/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(13%) 3/23	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(1%) 2/19 (1*/2)	MSA	Prospective, follow-up	NA	[5] Yoon, 2018
	(0.7%) 1/140	SND	Literature review	140	[7] Rivest et al., 1990
Laryngeal	(49%) 33/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(0.7%) 1/140	OPCA	Literature review	140	[7] Rivest et al., 1990
Trunk	(42%) 24/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(26%) 5/19	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
	(22%) 15/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(4%) 1/23	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(1%) 2/191 (0*/2)	MSA	Prospective follow-up	NA	[5] Yoon, 2018
	(0.7%) 1/140	SND	Literature review	140	[7] Rivest et al., 1990
Stridor	(37%) 25/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(34%) 34/100	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
	(26%) 19/73	MSA-P	Multicenter Cross-sectional	NA	[18] Moreno-Lopez, 2011
	(22%) 15/67	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
	(15%) 2/13	MSA-C	Multicenter Cross-sectional	NA	[18] Moreno-Lopez, 2011

MSA, multiple system atrophy; MSA-P, parkinsonian subtype; MSA-C, cerebellar subtype; OPCA, olivopontocerebellar atrophy; SND, striatonigral degeneration; NS, not specified; NA, not assessed. * Levodopa induced. Note that studies conducted up to 1995 are based on the following diagnostic criteria: Graham and Oppenheimer, 1969 and/or Quinn, 1989 [107,108]; whereas all the studies conducted after 1998 are based on the criteria provided by Gilman et al., 1998 [109].

commonly reported form of dystonia in DLB [53–55], occurring in up to 25% of pathology-confirmed cases [53].

Uncommon dystonic manifestations in DLB may affect the cervical region (anterocollis) and the tongue as side effects of dopaminergic, cholinergic or neuroleptic medications, promptly reversed by discontinuation of the causative drug [56–59].

3. Pathophysiology

The pathophysiology of dystonia in APD has not been directly investigated. Inferences on dystonia pathophysiology in APD may be drawn from clinical observations, such as in the relationship between dystonia and dopaminergic medications in these conditions. Clinical observations suggest that limb dystonia disappears after initiation of therapy in levodopa-responsive MSA patients, reflecting a prominent role of nigrostriatal dysfunction over postsynaptic striatal pathology [10,60]. On the other hand, the mechanisms must be different for the lower facial and jaw dystonia of MSA and for other dystonic features in PSP, CBS and DLB in which dystonia is induced rather than ameliorated by levodopa [9,50–52,56–59].

Earlier clinicopathological studies provided clear evidence of basal ganglia involvement in dystonia caused by stroke and other focal lesions [61]. Thus, neurodegenerative phenomena within the basal ganglia in APD likely represent the most important determinant of dystonia in these conditions. The appearance of dystonia in the same anatomical regions as parkinsonian features in APD, however, may be viewed as a paradox of the functional model of basal ganglia function, which predicts that basal ganglia inhibitory output toward the thalamus is increased in parkinsonism but decreased in dystonia [62]. The co-occurrence of dystonia and parkinsonism in the same body part may reflect a greater disruption in the sensorimotor network, which, in addition to the basal ganglia includes the motor cortex, the brainstem and the cerebellum, and their connections [63,64].

Primary dystonia is characterized by enhanced excitability and loss of inhibition at several anatomical levels, including sensorimotor cortex, brainstem and spinal cord. Notably, loss of intracortical inhibition has been demonstrated also in secondary dystonia due to basal ganglia lesions, which share pathological topography with dystonia in APD [65]. However, there is lack of neurophysiological studies on dystonia in APD. Neurophysiological studies based on transcranial magnetic stimulation and other techniques in APD have revealed enhanced excitability at cortical and brainstem levels without controlling for presence of dystonia [6]. Increased cortical excitability in APD may result from the loss of inhibitory input from non-primary motor areas, similarly as in PD, or loss of somatosensory-motor cortex input, as in CBS due to parietal lobe involvement [6,66]. Alternative mechanisms may include the loss of inhibitory interneurons in the cortex or thalamus, as demonstrated in PSP [6,67,68]. Another neurophysiological

Table 2
Frequency and distribution of different types of dystonia in PSP.

Dystonia Type	Dystonia Frequency	Disease subtype	Study Type	Pathologic confirmation (n°patients)	Author(s)
Blepharospasm	(100%) 7/7	PSP	Cross-sectional	NA	[35] Krack and Marion, 1994
	(33%) 2/6 1*/2	PSP	Retrospective chart review	NA	[30] Lamberti et al., 2002
	(26%) 10/38	PSP	Cross-sectional	NA	[28] Golbe et al., 1989
	(24%) 20/83 (1*/20)	PSP	Retrospective chart review	NA	[33] Barclay & Lang, 1997
	(10%) 6/57	PSP	Retrospective chart review	NA	[32] Rana et al., 2012
Other craniofacial/Oromandibular	(29%) 8*/27	PSP	Prospective	NA	[5] Yoon, 2018
	(3%) 3/83	PSP	Retrospective chart review	NA	[33] Barclay & Lang, 1997
	(12%) 1/8	PSP	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(2%) 2/118	PSP	Literature review	118	[7] Rivest et al., 1990
	(26%) 22/83 9/22 hemi dystonia	PSP	Retrospective chart review	NA	[33] Barclay & Lang, 1997
Limb	(26%) 8/30 (3*/8)	PSP	Retrospective chart review	NA	[42] Rafal and Friedman, 1987
	(25%) 2/8	PSP	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(19%) 15/77	PSP[§]	Retrospective chart review	77	[44] Respondek et al., 2014
	(5%) 6/118	PSP	Literature review	118	[7] Rivest et al., 1990
	(5%) 1/19	PSP	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Retrocollis	(25%) 2/8	PSP	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(17%) 14/83	PSP	Retrospective chart review	NA	[33] Barclay & Lang, 1997
Anterocollis	(10%) 2/19	PSP	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Cervical NS	(7%) 2/27	PSP	Prospective	NA	[5] Yoon, 2018
	(1%) 2/118	PSP	Literature review	118	[7] Rivest et al., 1990
Trunk	(19%) 15/77	PSP[§]	Retrospective chart review	77	[44] Respondek et al., 2014
	(5%) 1/19	PSP	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Dystonia (Type NA)	(5%) 6/118	PSP	Literature review	118	[7] Rivest et al., 1990

PSP, progressive supranuclear palsy; NS, not specified; NA, not available. * Levodopa induced. [§] PSP subtypes considered in the present article were: RS, Richardson's syndrome; PI, postural instability; OM, oculomotor; P, parkinsonism; CBS, corticobasal syndrome; FTD, frontotemporal dysfunction; Unclassified, patients not fitting any of these predominance types (The subtypes mostly associated with trunk dystonia were PSP-RS, followed by PSP-PI and PSP-FTD; the subtypes mostly associated with limb dystonia were PSP-CBS followed by PSP-P). Note that studies conducted up to 1987 are based on the following diagnostic criteria: Steele et al., 1964 [26]; studies conducted from 1989 to 1997 are based on the criteria provided by Maher and Lees, 1986 [110]; studies conducted in 2002–2003 and 2014-2018 are based on the criteria provided by Hauw et al., 1994 (NINDS criteria) [111]; and finally studies conducted from 2002 to 2012 are based on the criteria provided by Litvan et al., 1996 [112].

finding in primary dystonia is an abnormally enhanced plasticity [64,69]. While enhanced plasticity has been documented in PSP patients, abnormally reduced plasticity have been observed in MSA and CBS patients; all these studies, however, did not control for dystonic features [6,67,68]. Finally, neurophysiological assessments in PSP and MSA support the hypothesis of cerebellar dysfunction as a plausible mechanism involved in the generation of dystonia in these disorders. Data are lacking for CBD and DLB [6].

In summary, despite the scarcity of dedicated studies, neurodegenerative mechanisms along with neurophysiological changes at cortical, brainstem and cerebellar levels are all putative pathophysiological mechanisms involved in dystonia generation in APD. Either the dysfunction of specific nodes (basal ganglia, motor cortex and cerebellum) or an abnormal interaction between these systems through the networks in which they operate may explain the variable phenomenology of dystonia in APD.

4. Diagnostic clues

The recognition of specific dystonic features, including their prevalence, topographic distribution, and relationship with dopaminergic therapy, may all assist in distinguishing among different APD or

Table 3
Frequency and distribution of different types of dystonia in CBS/CBD.

Dystonia Type	Dystonia Frequency	Disease Subtype	Study Type	Pathologic confirmation (n°patients)	Author(s)
Limb	(100%) 7/7	CBD	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(80%) 118/147	CBD	Retrospective chart review	6	[45] Kompoliti et al., 1998
	(66%) 10/15 (1*/10)	CBS	Prospective, 5 y follow-up	NA	[5] Yoon, 2018
	(54%) 36/66	CBD	Retrospective chart review	NA	[46] Vanek et al., 2001
	(17%) 65/374	CBD	Literature review	374	[49] Stamelou et al., 2012
	(16%) 11/66	CBD	Retrospective chart review	NA	[46] Vanek et al., 2001
	(14%) 5/35	CBD	Retrospective chart review	35	[51] Ling et al., 2010
Dystonia (NA)	(71%) 105/147	CBD	Retrospective chart review	7	[45] Kompoliti et al., 1998
Head, neck or trunk dystonia	(18%) 12/66	CBD	Retrospective chart review	NA	[46] Vanek et al., 2001
Blepharospasm	(14%) 1/7	CBD	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
	(1.9%) 7/374	CBD	Literature review	374	[49] Stamelou et al., 2012
Retrocollis	(14%) 1/7	CBD	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
Cervical NS	(2%) 8/374	CBD	Literature review	374	[49] Stamelou et al., 2012

CBS, corticobasal syndrome; CBD, corticobasal degeneration; NS, not specified; NA, not available. * Levodopa induced. Diagnostic criteria, when specified, were based on the criteria provided by Gibb et al., 1989 [113].

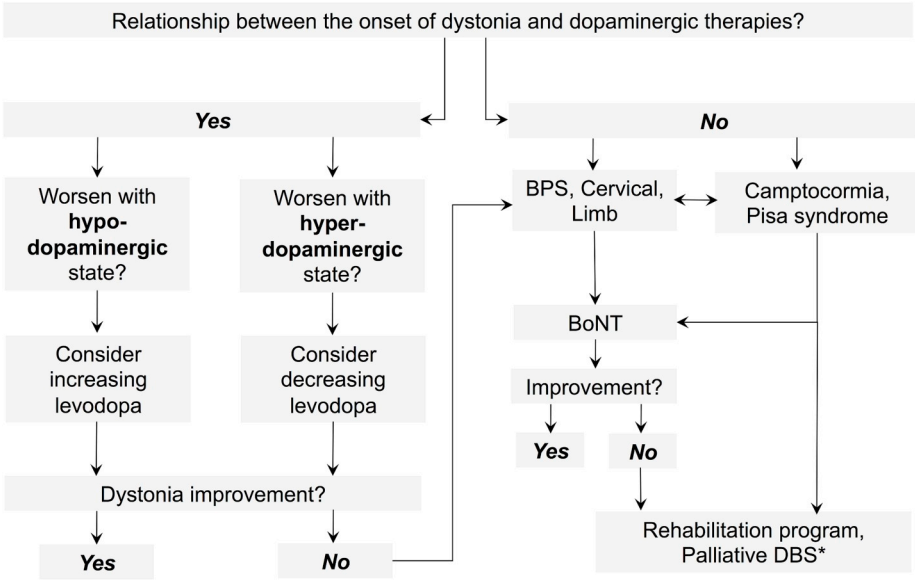

Fig. 2. Suggested anti-dystonic treatment approach in atypical parkinsonian disorders. Note that levodopa has been associated with improvement of foot dystonia, but with worsening of anterocollis in MSA patients [10], and with no improvement of dystonia in CBS patients [113]. The benefits of BoNT have been documented for focal dystonias in MSA, PSP, and CBS [33,45,114–117]. *DBS is only to be considered for exceptional cases. BPS, blepharospasm; BoNT, botulinum neurotoxin; DBS, deep brain stimulation.

between APD and PD. In general, dystonia is overall more frequent in APD than PD; in particular blepharospasm and anterocollis are far more common in APD (PSP for blepharospasm and MSA-P for anterocollis) than in PD [70].

Topography. Dystonia involving the orofacial region should raise suspicion for MSA, commonly drug-induced; it is present to a much lesser extent in DLB. Blepharospasm is vastly more frequent in PSP than in MSA [31,71]. Deepened nasolabial folds and furrowing of the forehead with a "reptilian stare" is a dystonic expression in PSP, a major red flag against any consideration for PD [9,37]. Anterocollis is more common in MSA-P; retrocollis in PSP [5]. Respiratory stridor, in the appropriate context, is nearly pathognomonic of MSA [11]. Marked forms of axial dystonia, namely camptocormia and Pisa syndrome, have been reported both in MSA-P and in PD patients [5], although the severity is greater and the latency to their development far shorter in MSA-P. Arm dystonia with the peculiar "pointing gun posture" is highly suggestive of PSP [33,42,43]. Finally, persistent unilateral dystonia as well as its persistence during sleep are considered diagnostic clue for CBS, based on a recent case series [72]. However it should be considered that there is a clinical-pathological overlap between PSP and CBS, and therefore it is not possible to differentiate PSP from CBD in clinical situations, where these are unattainable with currently available methods [51,73,74].

Relationship with levodopa. Early appearance of levodopa-induced orofacial dystonia is highly suggestive of MSA-P over PD (in which it may also occur, but later in the course) [75,76]. Conversely, cranial dystonia in PSP is largely unrelated to/unaffected by dopaminergic treatment [77], although rare cases of levodopa-induced oromandibular dystonia have been reported [12,39–41]. Levodopa-induced lower limb dystonia points in the direction of CBS, unlike PD in which lower limb dystonia tends to be improved by levodopa [12,45,49–52]. Indeed, PD dystonia represents a hypodopaminergic state in wearing-off states (e.g., nocturnal or early morning foot dystonia) or in the form of diphasic dyskinesia (e.g., beginning-of-dose and end-of-dose dyskinesia) [14,78–87]. Exceptions notwithstanding, dystonia in APD is often a presenting manifestation [10,11,36]; in PD, except for monogenic parkinsonism in which dystonia (particularly of the lower limb) may be seen earlier in the disease course, is an expression of advanced disease [70,75].

5. Special cases and dystonia mimics

Some clinical features in APD may mimic dystonia and are considered as pseudo-dystonia [88]. The distinction is critical to guide management strategies. Pisa syndrome and camptocormia should be distinguished from fixed orthopaedic deformities [20]. In PSP patients, the transient forced head deviation in the direction opposite to rotational head movements results from unopposed vestibulo-collic reflexes and may mimic torticollis [4]. Arm levitation in PSP or CBS may also be misinterpreted as dystonia [89]. Patients are unaware of the levitating arm but can readily bring it down on command, differentiating it from dystonia [89]. Despite the phenomenological overlap with arm levitation, the alien limb of CBS is held in an abnormal posture suggesting dystonia but with additional behaviors, for example, 'useless' grasping in anterior variant and withdrawal or hand-avoidance behaviour, often associated with hemianesthesia, hemianopia, or even anosognosia in the posterior variant.

Finally, it should be kept in mind that frequent pyramidal signs are present in APD. Thus, it may be sometimes difficult to differentiate between abnormal gait or posture due to dystonia versus due to spasticity in these patients.

6. Treatment

Therapeutic strategies for dystonia in APD consist of both pharmacological and non-pharmacological approaches (Fig. 2). If a close relationship between the onset of dystonia and dopaminergic therapies is ascertained, a dose reduction or drug discontinuation should be considered. Although levodopa can improve anterocollis in PD [14], such effect is partial or absent in MSA-P [10,45]. In addition, it has been proposed that muscle relaxants or benzodiazepines (e.g., clonazepam) might also be helpful in alleviating dystonic symptoms [14]. Pisa syndrome has been treated with anticholinergics and clozapine with limited efficacy [90]. Amantadine, propranolol, primidone, bromocriptine, amitryptiline, levetiracetam and valproate have provided limited or no benefit, and none of these agents have been examined in randomized clinical trials for the treatment of dystonia in APD [45,91].

BoNT can alleviate focal dystonia in APD to a greater extent than oral pharmacological treatments [33,92–94]. BoNT may also be considered for attenuating blepharospasm and lower face dystonia, particularly in the orofacial dystonia induced by levodopa in MSA-P [95], as this side effect may limit levodopa dose optimization. BoNT injected into deep neck flexors (e.g., *longus colli and longus capitis*) under ultrasound or CT guidance has been demonstrated to be beneficial in idiopathic cervical dystonia (anterocollis) [96]. Other neck muscles, namely the scalene and submental groups, might contribute to anterocollis; hence the therapeutic approach should be individualized in patients. As a general consideration, due to the involvement of deep

neck flexors BoNT treatment may be difficult in a significant proportion of these patients. Dysphagia is a dose-limiting side effect. BoNT injections may also be effective in severe retrocollis in PSP, particularly when painful. A small-blinded crossover trial comparing BoNT injections into the lumbar paraspinal muscles versus placebo in PD patients with Pisa syndrome showed significant improvement in posture after BoNT [85]. However, these results have not yet been replicated in other centers, and this approach cannot be recommended at the moment [95,97]. Finally, although BoNT injections are unlikely to improve hand function, they may be useful for hygiene purposes in APD.

Besides pharmacotherapy and BoNT chemo denervation, exercise programs for coordination and posture using grasping, rolling over in bed and verbal/visual feedback may have modest effects [36,98,99]. In particular, physical therapy may be useful to prevent or minimize contracture [98]. Surgical fusion [100] and deep brain stimulation (DBS) [101–105] may only be considered palliative in exceptional cases. In PSP, a few cases of pedunculopontine nucleus DBS have shown modest improvement on dystonic symptoms [106].

7. Conclusions and next steps

Dystonia is a common manifestation of APD. In addition to the deformity it causes, dystonia reduces motor dexterity and interferes with gait, increases the likelihood of falling, and can produce discomfort and pain, thus increasing overall functional disability [106]. The varying prevalence of dystonia reported across APD may in part be due to a combination of ascertainment biases, scarcity of pathology-proven diagnosis, and misdiagnoses. Future studies should better address the occurrence of dystonia in various APD subtypes, which is still an under-investigated issue. Greater understanding of the underlying pathophysiological mechanisms and biology of dystonia subtypes in APD could facilitate future therapeutic clinical trials and ultimately improve the management of this source of disability in patients with APD.

Conflicts of interest

The authors disclose no conflicts of interest regarding this manuscript.

Documentation of author roles

Conception and design: LM, MB, CC.

Acquisition of data: LM, MB, MK.

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Patient consent (including the consent to Be videoed/portrayed for publication)

Patients provided written consent to the publication of their images and videos, both in print and online (Internet).

Ethics approval

N/A.

Appendix A. Video 1

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References

[1] L. Marsili, C. Colosimo, Dystonia in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, in: P. Kanovsky, P.K.P. Bhatia, R.L. Rosales (Eds.), Dystonia and Dystonic Syndromes, Springer-Verlag, Wien, 2015, pp. 89–99.

[2] M.J. Armstrong, I. Litvan, A.E. Lang, T.H. Bak, K.P. Bhatia, B. Borroni, A.L. Boxer, D.W. Dickson, M. Grossman, M. Hallett, K.A. Josephs, A. Kertesz, S.E. Lee, B.L. Miller, S.G. Reich, D.E. Riley, E. Tolosa, A.I. Tröster, M. Vidailhet, W.J. Weiner, Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (2013) 496–503.

[3] L. Wermuth, X. Cui, N. Greene, E. Schernhammer, B. Ritz, Medical record review to differentiate between idiopathic Parkinson's disease and parkinsonism: a Danish record linkage study with 10 Years of follow-up, Parkinsons Dis (2015) 781479.

[4] R. Bhidayasiri, J. Sringean, S.G. Reich, C. Colosimo, Red flags phenotyping: a systematic review on clinical features in atypical parkinsonian disorders, pii, Park. Relat. Disord. (18) (2018) S1353–S8020, https://doi.org/10.1016/j.parkreldis.2018.10.009 30437-1.

[5] W.T. Yoon, Comparison of dystonia between Parkinson's disease and atypical parkinsonism: the clinical usefulness of dystonia distribution and characteristics in the differential diagnosis of parkinsonism, Neurol. Neurochir. Pol. 52 (2018) 48–53, https://doi.org/10.1016/j.pjnns.2017.11.004.

[6] M. Bologna, A. Suppa, F. Di Stasio, A. Conte, G. Fabbrini, A. Berardelli, Neurophysiological studies on atypical parkinsonian syndromes, Park. Relat. Disord. 42 (2017) 12–21.

[7] J. Rivest, N. Quinn, C.D. Marsden, Dystonia in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy, Neurology 40 (1990) 1571–1578.

[8] G.K. Wenning, F. Geser, W. Poewe, The 'risus sardonicus' of multiple system atrophy, Mov. Disord. 18 (2003) 1211.

[9] G. Fabbrini, G. Defazio, C. Colosimo, P.D. Thompson, A. Berardelli A, Cranial movement disorders: clinical features, pathophysiology, differential diagnosis and treatment, Nat. Clin. Pract. Neurol. 5 (2009) 93–105.

[10] S.M. Boesch, G.K. Wenning, G. Ransmayr, W. Poewe, Dystonia in multiple system atrophy, J. Neurol. Neurosurg. Psychiatry 72 (2002) 300–303.

[11] M. Kollensperger, F. Geser, K. Seppi, M. Stampfer-Kountchev, M. Sawires, C. Scherfler, S. Boesch, J. Mueller, V. Koukouni, N. Quinn, M.T. Pellecchia, P. Barone, N. Schimke, R. Dodel, W. Oertel, E. Dupont, K. Østergaard, C. Daniels, G. Deuschl, T. Gurevich, N. Giladi, M. Coelho, C. Sampaio, C. Nilsson, H. Widner, F.D. Sorbo, A. Albanese, A. Cardozo, E. Tolosa, M. Abele, T. Klockgether, C. Kamm, T. Gasser, R. Djaldetti, C. Colosimo, G. Meco, A. Schrag, W. Poewe, G.K. Wenning, European MSA study group, red flags for multiple system Atrophy, Mov. Disord. 23 (2008) 1093–1099.

[12] C. Godeiro-Junior, A.C. Felício, O.G. Barsottini, P.M. Aguiar, S.M. Silva, V. Borges, H.B. Ferraz, Clinical features of dystonia in atypical parkinsonism, Arq. Neuropsiquiatr. 66 (2008) 800–804.

[13] R. Ashour, J. Jankovic, Joint and skeletal deformities in Parkinson's disease, multiple system Atrophy, and progressive supranuclear palsy, Mov. Disord. 21 (2006) 1856–1863.

[14] K. Kashihara, M. Ohno, S. Tomita, Dropped head syndrome in Parkinson's disease, Mov. Disord. 21 (2006) 1213–1216.

[15] G.K. Wenning, Y. Ben Shlomo, M. Magalhaes, S.E. Daniel, N.P. Quinn, Clinical features and natural history of multiple system atrophy. An analysis of 100 cases,

Brain 117 (1994) 835–845.
[16] G.K. Wenning, Y. Ben Shlomo, M. Magalhaes, S.E. Daniel, N.P. Quinn, Clinicopathological study of 35 cases of multiple system atrophy, J. Neurol. Neurosurg. Psychiatry 58 (1995) 160–166.
[17] G.K. Wenning, F. Tison, Y. Ben Shlomo, S.E. Daniel, N.P. Quinn, Multiple system atrophy: a review of 203 pathologically proven cases, Mov. Disord. 12 (1997) 133–147.
[18] C. Moreno-López, J. Santamaría, M. Salamero, F. Del Sorbo, A. Albanese, M.T. Pellecchia, P. Barone, S. Overeem, B. Bloem, W. Aarden, M. Canesi, A. Antonini, S. Duerr, G.K. Wenning, W. Poewe, A. Rubino, G. Meco, S.A. Schneider, K.P. Bhatia, R. Djaldetti, M. Coelho, C. Sampaio, V. Cochen, H. Hellriegel, G. Deuschl, C. Colosimo, L. Marsili, T. Gasser, E. Tolosa, Excessive daytime sleepiness in multiple system atrophy (SLEEMSA study), Arch. Neurol. 68 (2011) 223–230, https://doi.org/10.1001/archneurol.2010.359.
[19] F.J. Schwab, V.A. Smith, M. Biserni, L. Gamez, J.P. Farcy, M. Pagala, Adult scoliosis: a quantitative radiographic and clinical analysis, Spine 27 (2002) 387–392.
[20] K.M. Doherty, B.P. van de Warrenburg, M.C. Peralta, L. Silveira-Moriyama, J.P. Azulay, O.S. Gershanik, B.R. Bloem, Postural deformities in Parkinson's disease, Lancet Neurol. 10 (2011) 538–549.
[21] K. Kashihara, T. Imamura, Clinical correlates of anterior and lateral flexion of the thoracolumbar spine and dropped head in patients with Parkinson's disease, Park. Relat. Disord. 18 (2012) 290–293.
[22] D. Tiple, G. Fabbrini, C. Colosimo, D. Ottaviani, F. Camerota, G. Defazio, A. Berardelli, Camptocormia in Parkinson disease: an epidemiological and clinical study, J. Neurol. Neurosurg. Psychiatry 80 (2009) 145–148.
[23] K. Ekbom, H. Lindholm, L. Ljungberg, New dystonic syndrome associated with butyrophenone therapy, Z. Neurol. 202 (1972) 94–103.
[24] C. Colosimo, Pisa syndrome in a patient with multiple system atrophy, Mov. Disord. 13 (1998) 607–609.
[25] S. Wijemanne, J. Jankovic, Hand, foot, and spine deformities in parkinsonian disorders, J. Neural Transm. 126 (2019) 253-264.
[26] J.C. Steele, J.C. Richardson, J. Olszewski, Progressive Supranuclear Palsy, A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia, Arch. Neurol. 10 (1964) 333–359.
[27] D.D. Pfaffenbach, D.D. Layton, T.P. Kearns, Ocular manifestations in progressive supranuclear palsy, Am. J. Ophthalmol. 74 (1972) 1179–1184.
[28] L.I. Golbe, P.H. Davis, F.E. Lepore, Eyelid movement abnormalities in progressive supranuclear palsy, Mov. Disord. 4 (1989) 297–302.
[29] J. Jankovic, D.I. Friedman, F.J. Pirozzolo, Progressive supranuclear palsy: motor, neurobehavioural and neuro-ophthalmological findings, in: M.B. Streifler, A.D. Korczyn, E. Melamed, M.B.H. Youdim (Eds.), Advances in Neurology, Raven Press, New York, 1990, pp. 293–304.
[30] P. Lamberti, M. De Mari, A. Zenzola, M.S. Aniello, G. Defazio, Frequency of apraxia of eyelid opening in the general population and in patients with extrapyramidal disorders, Neurol. Sci. 23 (2002) 81–82.
[31] W.T. Yoon, E.J. Chung, S.H. Lee, B.J. Kim, W.Y. Lee, Clinical analysis of blepharospasm and apraxia of eyelid opening in patients with parkinsonism, J. Clin. Neurol. 1 (2005) 159–165, https://doi.org/10.3988/jcn.2005.1.2.159.
[32] A.Q. Rana, A. Kabir, O. Dogu, A. Patel, S. Khondker, Prevalence of blepharospasm and apraxia of eyelid opening in patients with parkinsonism, cervical dystonia and essential tremor, Eur. Neurol. 68 (2012) 318–321, https://doi.org/10.1159/000341621.
[33] C.L. Barclay, A.E. Lang, Dystonia in progressive supranuclear palsy, J. Neurol. Neurosurg. Psychiatry 62 (1997) 352–356.
[34] D. Boghen, Apraxia of lid opening: a review, Neurology 48 (1997) 1491–1494.
[35] P. Krack, M.H. Marion, "Apraxia of lid opening", a focal eyelid dystonia: clinical study of 32 patients, Mov. Disord. 9 (1994) 610–615.
[36] C. Colosimo, D.E. Riley, G.K. Wenning, Handbook of Atypical Parkinsonism, Cambridge University Press, Cambridge, 2011.
[37] S. Romano, C. Colosimo, Procerus sign in progressive supranuclear palsy, Neurology 57 (2001) 1928.
[38] M. Bologna, G. Fabbrini, L. Marsili, G. Defazio, P.D. Thompson, A. Berardelli, Facial bradykinesia, J. Neurol. Neurosurg. Psychiatry 84 (2013) 681–685.
[39] E.K. Tan, L.L. Chan, M.C. Wong, Levodopa-induced oromandibular dystonia in progressive supranuclear palsy, Clin. Neurol. Neurosurg. 105 (2003) 132–134.
[40] A.E. Lang, Treatment of progressive supranuclear palsy and corticobasal degeneration, Mov. Disord. 12 (2005) S83–S91.
[41] E.J. Chung, S.J. Kim, Levodopa-induced facial dystonia in a case of progressive supranuclear palsy, J. Mov. Disord. 5 (2012) 28–32, https://doi.org/10.14802/jmd.12008.
[42] R.D. Rafal, J.H. Friedman, Limb dystonia in progressive supranuclear palsy, Neurology 37 (1987) 1545–1549.
[43] T. Oide, S. Ohara, M. Yazawa, K. Inoue, N. Itoh, T. Tokuda, S. Ikeda, Progressive supranuclear palsy with asymmetric tau pathology presenting with unilateral limb dystonia, Acta Neuropathol. 104 (2002) 209–214.
[44] G. Respondek, M. Stamelou, C. Kurz, L.W. Ferguson, A. Rajput, W.Z. Chiu, J.C. van Swieten, C. Troakes, S. Al Sarraj, E. Gelpi, C. Gaig, E. Tolosa, W.H. Oertel, A. Giese, S. Roeber, T. Arzberger, S. Wagenpfeil, G.U. Höglinger, Movement Disorder Society-endorsed PSP Study Group, the phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases, Mov. Disord. 29 (2014) 1758–1766, https://doi.org/10.1002/mds.26054.
[45] K. Kompoliti, C.G. Goetz, B.F. Boeve, D.M. Maraganore, J.E. Ahlskog, C.D. Marsden, K.P. Bhatia, P.E. Greene, S. Przedborski, E.C. Seal, R.S. Burns, R.A. Hauser, L.L. Gauger, S.A. Factor, E.S. Molho, D.E. Riley, Clinical presentation and pharmacological therapy in corticobasal degeneration, Arch. Neurol. 55 (1998) 957–961.
[46] Z. Vanek, J. Jankovic, Dystonia in corticobasal degeneration, Mov. Disord. 16 (2001) 252–257.
[47] C. Halpern, C. McMillan, P. Moore, K. Dennis, M. Grossman, Calculation impairment in neurodegenerative diseases, J. Neurol. Sci. 208 (2003) 31–38.
[48] L.M. Chahine, T. Rebeiz, J.J. Rebeiz, M. Grossman, R.G. Gross, Corticobasal syndrome: five new things, Neurol. Clin. Pract. 4 (2014) 304–312, https://doi.org/10.1212/CPJ.0000000000000026.
[49] M. Stamelou, A. Alonso-Canovas, K.P. Bhatia, Dystonia in corticobasal degeneration: a review of the literature on 404 pathologically proven cases, Mov. Disord. 27 (2012) 696–702.
[50] J. Horvath, E. Kövari, C. Bouras, P.R. Burkhard, Neuropathological correlates of lower limb corticobasal degeneration, Neuropathol. Appl. Neurobiol. 35 (2009) 623–627.
[51] H. Ling, S.S. O'sullivan, J.L. Holton, T. Revesz, L.A. Massey, D.R. Williams, D.C. Paviour, A.J. Lees, Does corticobasal degeneration exist? A clinicopathological re-evaluation, Brain 133 (2010) 2045–2057.
[52] N. Kouri, J.L. Whitwell, K.A. Josephs, R. Rademakers, D.W. Dickson, Corticobasal degeneration: a pathologically distinct 4R tauopathy, Nat. Rev. Neurol. 7 (2011) 263–272.
[53] M.H. Mark, J.I. Sage, D.W. Dickson, R.E. Heikkila, L. Manzino, K.O. Schwarz, R.C. Duvoisin, Meige syndrome in the spectrum of Lewy body disease, Neurology 44 (1994) 1432–1436.
[54] N. Tabet, S. Sivaloganathan, Meige's syndrome in dementia with Lewy bodies, J. R. Soc. Med. 95 (2002) 201–202.
[55] L.K. Chan, Y.H. Ho, C.S. Yu, Dementia with Lewy bodies in meige syndrome, Innov. Clin. Neurosci. 9 (2012) 39–41.
[56] M.J. Aries, H. Debruyne, S. Engelborghs, N. Le Bastard, N. Somers, D. Gorissen, B.A. Pickut, P.P. De Deyn, Reversal of head drop after discontinuation of olanzapine in a DLB patient, Mov. Disord. 23 (2008) 1760–1762, https://doi.org/10.1002/mds.22182.
[57] N. Hasegawa, K. Shimada, Y. Yamamoto, K. Maeda, Case of dementia with Lewy bodies showing cervical dystonia after donepezil administration, Rinsho Shinkeigaku 50 (2010) 147–150.
[58] K. Tanaka, I. Wada, T. Okunomiya, A. Shima, D. Kambe, A. Shinde, T. Kageyama, T. Suenaga, Dropped head syndrome preceding the onset of dementia with Lewy bodies, Intern. Med. 53 (2014) 883–886.
[59] Y. Shiga, Y. Kanaya, R. Kono, S. Takeshima, Y. Shimoe, M. Kuriyama, Dementia with Lewy bodies presenting marked tongue protrusion and bite due to lingual dystonia: a case report, Rinsho Shinkeigaku 56 (2016) 418–423.
[60] W. Poewe, G.K. Wenning, The natural history of Parkinson's disease, Ann. Neurol. 44 (1998) 1–9.
[61] K.P. Bhatia, C.D. Marsden, The behavioural and motor consequences of focal lesions of the basal ganglia in man, Brain 117 (1994) 859–876.
[62] M.R. DeLong, T. Wichmann, Circuits and circuit disorders of the basal ganglia, Arch. Neurol. 64 (2007) 20–24 PubMed PMID: 17210805.
[63] C.N. Prudente, E.J. Hess, H.A. Jinnah, Dystonia as a network disorder: what is the role of the cerebellum? Neuroscience 260 (2014) 23–35, https://doi.org/10.1016/j.neuroscience.2013.11.062.
[64] A. Quartarone, M. Hallett, Emerging concepts in the physiological basis of dystonia, Mov. Disord. 28 (2013) 958–967.
[65] M. Kojovic, I. Pareés, P. Kassavetis, F.J. Palomar, P. Mir, J.T. Teo, C. Cordivari, J.C. Rothwell, K.P. Bhatia, M.J. Edwards, Secondary and primary dystonia: pathophysiological differences, Brain 136 (2013) 2038–2049, https://doi.org/10.1093/brain/awt150.
[66] M. Bologna, G. Leodori, P. Stirpe, G. Paparella, D. Colella, D. Belvisi, A. Fasano, G. Fabbrini, A. Berardelli, Bradykinesia in early and advanced Parkinson's disease, J. Neurol. Sci. 369 (2016) 286–291, https://doi.org/10.1016/j.jns.2016.08.028.
[67] A. Conte, D. Belvisi, M. Bologna, D. Ottaviani, G. Fabbrini, C. Colosimo, D.R. Williams, A. Berardelli, Abnormal cortical synaptic plasticity in primary motor area in progressive supranuclear palsy, Cerebr. Cortex 22 (2012) 693–700.
[68] M. Bologna, K. Bertram, G. Paparella, C. Papi, D. Belvisi, A. Conte, A. Suppa, D.R. Williams, A. Berardelli, Reversal of long term potentiation-like plasticity in primary motor cortex in patients with progressive supranuclear palsy, Clin. Neurophysiol. 128 (2017) 1547–1552.
[69] P. Calabresi, A. Pisani, J. Rothwell, V. Ghiglieri, J.A. Obeso, B. Picconi, Hyperkinetic disorders and loss of synaptic downscaling, Nat. Neurosci. 19 (2016) 868–875.
[70] A.S. Shetty, K.P. Bhatia, A.E. Lang, Dystonia and Parkinson's disease: what is the relationship? pii: S0969-9961(19)30107-X, Neurobiol. Dis. (2019), https://doi.org/10.1016/j.nbd.2019.05.001 [Epub ahead of print].
[71] G.U. Höglinger, G. Respondek, M. Stamelou, C. Kurz, K.A. Josephs, A.E. Lang, B. Mollenhauer, U. Müller, C. Nilsson, J.L. Whitwell, T. Arzberger, E. Englund, E. Gelpi, A. Giese, D.J. Irwin, W.G. Meissner, A. Pantelyat, A. Rajput, J.C. van Swieten, C. Troakes, A. Antonini, K.P. Bhatia, Y. Bordelon, Y. Compta, J.C. Corvol, C. Colosimo, D.W. Dickson, R. Dodel, L. Ferguson, M. Grossman, J. Kassubek, F. Krismer, J. Levin, S. Lorenzl, H.R. Morris, P. Nestor, W.H. Oertel, W. Poewe, G. Rabinovici, J.B. Rowe, G.D. Schellenberg, K. Seppi, T. van Eimeren, G.K. Wenning, A.L. Boxer, L.I. Golbe, I. Litvan, Movement Disorder Society-endorsed PSP Study Group, Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria, Mov. Disord. 32 (2017) 853–864, https://doi.org/10.1002/mds.26987.
[72] R. Infante, E. Antelmi, F. Pizza, M. Stanzani Maserati, G. Plazzi, G. Rizzo, R. Liguori, Persistence of limb dystonia and myoclonus during sleep in corticobasal syndrome: a case series, pii: S1389–9457(18)30709-3, Sleep Med. (2019), https://doi.org/10.1016/j.sleep.2018.12.025 [Epub ahead of print].

[73] G.U. Höglinger, Is it useful to classify progressive supranuclear palsy and corticobasal degeneration as different disorders? No, mov. Disord, Clin. Pract. 5 (2018) 141–144, https://doi.org/10.1002/mdc3.12582.
[74] M.J. Grimm, G. Respondek, M. Stamelou, T. Arzberger, L. Ferguson, E. Gelpi, A. Giese, M. Grossman, D.J. Irwin, A. Pantelyat, A. Rajput, S. Roeber, J.C. van Swieten, C. Troakes, A. Antonini, K.P. Bhatia, C. Colosimo, T. van Eimeren, J. Kassubek, J. Levin, W.G. Meissner, C. Nilsson, W.H. Oertel, I. Piot, W. Poewe, G.K. Wenning, A. Boxer, L.I. Golbe, K.A. Josephs, I. Litvan, H.R. Morris, J.L. Whitwell, Y. Compta, J.C. Corvol, A.E. Lang, J.B. Rowe, G.U. Höglinger, Movement Disorder Society-endorsed PSP Study Group, How to apply the movement disorder society criteria for diagnosis of progressive supranuclear palsy, Mov. Disord. (2019), https://doi.org/10.1002/mds.27666.
[75] D. Martino, A.J. Espay, A. Fasano, F. Morgante, Disorders of Movement, A Guide to Diagnosis and Treatment, Springer-Verlag, Berlin Heidelberg, 2016, pp. 4–6, https://doi.org/10.1007/978-3-662-48468-5.
[76] A.J. Espay, F. Morgante, A. Merola, A. Fasano, L. Marsili, S.H. Fox, E. Bezard, B. Picconi, P. Calabresi, A.E. Lang, Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts, Ann. Neurol. (2018), https://doi.org/10.1002/ana.25364.
[77] D.R. Williams, A.J. Lees, What features improve the accuracy of the clinical diagnosis of progressive supranuclear palsy-parkinsonism (PSP-P)? Mov. Disord. 25 (2010) 357–362, https://doi.org/10.1002/mds.22977.
[78] D.O. Corbin, A.C. Williams, Stridor during dystonic phases of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 50 (1987) 821–822.
[79] M.R. Luquin, O. Scipioni, J. Vaamonde, O. Gershanik, J.A. Obeso, Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification, Mov. Disord. 7 (1992) 117–124.
[80] H. Yamada, Y. Katayama, T. Yamamoto, Parkinson's disease and dropped head, Rinsho Shinkeigaku 43 (2003) 955.
[81] K. Fujimoto, Dropped head in Parkinson's disease, J. Neurol. 253 (2006) 21–26.
[82] J.E. Rice, R. Antic, P.D. Thompson, Disordered respiration as a levodopa-induced dyskinesia in Parkinson's disease, Mov. Disord. 17 (2002) 524–527.
[83] M. Merello, I.T. Damas, J.A. Obeso, Features and mechanisms of diphasic dyskinesia in Parkinson's disease, in: S. Fox, J.M. Brotchie (Eds.), Levodopa-induced Dyskinesia in Parkinson's Disease, Springer-Verlag, London, 2014(Chapter 8).
[84] R. Bhidayasiri, O. Jitkritsadakul, C. Colosimo, Nocturnal manifestations of atypical parkinsonian disorders, J. Parkinson's Dis. 4 (2014) 223–236, https://doi.org/10.3233/JPD-130280.
[85] P. Zis, K.R. Chaudhuri, M. Samuel, Phenomenology of levodopa-induced dyskinesia, in: S. Fox, J.M. Brotchie (Eds.), Levodopa-induced Dyskinesia in Parkinson's Disease, Springer-Verlag, London, 2014(Chapter 1).
[86] L. Verhagen Metman, A.J. Espay, Teaching Video NeuroImages: the underrecognized diphasic dyskinesia of Parkinson disease, Neurology 89 (2017) e83–e84, https://doi.org/10.1212/WNL.0000000000004238.
[87] C.G. Goetz, G.T. Stebbins, L. Wang, N.R. LaPelle, S. Luo, B.C. Tilley, IPMDS-sponsored scale translation program: process, format, and clinimetric testing plan for the MDS-UPDRS and UDysRS, Mov. Disord. Clin Pract. 1 (2014) 97–101.
[88] A. Albanese, K. Bhatia, S.B. Bressman, M.R. Delong, S. Fahn, V.S. Fung, M. Hallett, J. Jankovic, H.A. Jinnah, C. Klein, A.E. Lang, J.W. Mink, J.K. Teller, Phenomenology and classification of dystonia: a consensus update, Mov. Disord. 28 (2013) 863–873, https://doi.org/10.1002/mds.25475.
[89] M. Kojovi, K.P. Bhatia, Bringing order to higher order motor disorders, J. Neurol. (2018), https://doi.org/10.1007/s00415-018-8974-9.
[90] L. Bonanni, A. Thomas, S. Varanese, V. Scorrano, M. Onofrj, Botulinum toxin treatment of lateral axial dystonia in Parkinsonism, Mov. Disord. 22 (2007) 2097–2103.
[91] D. Tiwari, K. Amar, A case of corticobasal degeneration presenting with alien limb syndrome, Age Ageing 37 (2008) 600–601, https://doi.org/10.1093/ageing/afn103.
[92] N. Giagkou, M. Stamelou, Therapeutic management of the overlapping syndromes of atypical parkinsonism, CNS Drugs 32 (2018) 827–837, https://doi.org/10.1007/s40263-018-0551-3.
[93] J. Jankovic, An update on new and unique uses of botulinum toxin in movement disorders, Toxicon 147 (2018) 84-88.
[94] A. Jocson, M. Lew, Use of botulinum toxin in Parkinson's disease, Park. Relat. Disord. 59 (2019) 57–64, https://doi.org/10.1016/j.parkreldis.2018.12.002.
[95] F. Cardoso, Botulinum toxin in parkinsonism: the when, how, and which for botulinum toxin injections, Toxicon 147 (2018) 107-110.
[96] B. Herting, S. Wunderlich, T. Glockler, M. Bendszus, D. Mucha, H. Reichmann, M. Naumann, Computed tomographically-controlled injection of botulinum toxin into the longus colli muscle in severe anterocollis, Mov. Disord. 19 (2004) 588–590.
[97] K.L. Bertram, P. Stirpe, C. Colosimo, Treatment of camptocormia with botulinum toxin, Toxicon 107 (2015) 148–153, https://doi.org/10.1016/j.toxicon.2015.06.004.
[98] R. Formisano, L. Pratesi, F.T. Modarelli, V. Bonifati, G. Meco, Rehabilitation and Parkinson's disease, Scand. J. Rehabil. Med. 24 (1992) 157–160.
[99] C. Stallibrass, P. Sissons, C. Chalmers, Randomized controlled trial of the Alexander technique for idiopathic Parkinson's disease, Clin. Rehabil. 16 (2002) 695–708.
[100] E.A.C. Pereira, J. Wilson-MacDonald, A.L. Green, T.Z. Aziz, T.A. Cadoux-Hudson, Posterior occipitocervical instrumented fusion for dropped head syndrome after deep brain stimulation, J. Clin. Neurosci. 17 (2010) 541–542.
[101] L.N. Hazrati, J.C. Wong, C. Hamani, A.M. Lozano, Y.Y. Poon, J.O. Dostrovsky, W.D. Hutchison, C. Zadikoff, E. Moro, Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation, Mov. Disord. 27 (2012) 1304–1307.
[102] K.J. Bergmann, V.L. Salak, Subthalamic stimulation improves levodopa responsive symptoms in a case of progressive supranuclear palsy, Park. Relat. Disord. 14 (2008) 348–352.
[103] P.K. Doshi, J.D. Desai, B. Karkera, P.M. Wadia, Bilateral peduncu- lopontine nucleus stimulation for progressive supranuclear palsy, Stereotact. Funct. Neurosurg. 93 (2015) 59–65.
[104] P. Santens, K. Vonck, M. De Letter, K. Van Driessche, A. Sieben, J. De Reuck, D. Van Roost, P. Boon, Deep brain stimulation of the internal pallidum in multiple system atrophy, Park. Relat. Disord. 12 (2006) 181–183 Erratum in: Parkinsonism Relat Disord. 2007 13 (1) 63.
[105] W.G. Meissner, C. Laurencin, C. Tranchant, T. Witjas, F. Viallet, D. Guehl, P. Damier, J.L. Houeto, F. Tison, A. Eusebio, A. Vital, N. Streichenberger, B. Lannes, A. Maues de Paula, S. Thobois, Outcome of deep brain stimulation in slowly progressive multiple system atrophy: a clinico-pathological series and review of the literature, Park. Relat. Disord. 24 (2016) 69–75, https://doi.org/10.1016/j.parkreldis.2016.01.005.
[106] D. Servello, E. Zekaj, C. Saleh, C. Menghetti, M. Porta, Long-term follow-up of deep brain stimulation of peduncolopontine nucleus in progressive supranuclear palsy: report of three cases, Surg. Neurol. Int. 5 (2014) 416–420, https://doi.org/10.4103/2152-7806.140208.
[107] J.G. Graham, D.R. Oppenheimer, Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy, J. Neurol. Neurosurg. Psychiatry 32 (1969) 28–34.
[108] N. Quinn, Disproportionate antecollis in multiple system atrophy, The Lancet 333 (1989) 844.
[109] S. Gilman, P. Low, N. Quinn, A. Albanese, Y. Ben-Shlomo, C.J. Fowler, H. Kaufmann, T. Klockgether, A.E. Lang, P.L. Lantos, I. Litvan, C.J. Mathias, E. Oliver, D. Robertson, I. Schatz, G.K. Wenning, Consensus statement on the diagnosis of multiple system atrophy, American Autonomic Society and American Academy of Neurology, Clin. Auton. Res. 8 (1998) 359–362.
[110] E.R. Maher, A.J. Lees, The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy), Neurology 36 (1986) 1005–1008.
[111] J.J. Hauw, S.E. Daniel, D. Dickson, D.S. Horoupian, K. Jellinger, P.L. Lantos, A. McKee, M. Tabaton, I. Litvan, Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy), Neurology 44 (1994) 2015–2019.
[112] I. Litvan, Y. Agid, D. Calne, G. Campbell, B. Dubois, R.C. Duvoisin, C.G. Goetz, L.I. Golbe, J. Grafman, J.H. Growdon, M. Hallett, J. Jankovic, N.P. Quinn, E. Tolosa, D.S. Zee, Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop, Neurology 47 (1996) 1–9.
[113] W.R. Gibb, P.J. Luthert, C.D. Marsden, Corticobasal degeneration, Brain 112 (1989) 1171–1192.
[114] I.M. Merlo, A. Occhini, C. Pacchetti, E. Alfonsi, Not paralysis, but dystonia causes stridor in multiple system atrophy, Neurology 58 (2002) 649–652.
[115] J. Müller, G.K. Wenning, J. Wissel, K. Seppi, W. Poewe, Botulinum toxin treatment in atypical parkinsonian disorders associated with disabling focal dystonia, J. Neurol. 249 (2002) 300–304.
[116] C. Cordivari, V.P. Misra, S. Catania, A.J. Lees, Treatment of dystonic clenched fist with botulinum toxin, Mov. Disord. 16 (2001) 907–913.
[117] H.S. Shehata, N.M. Shalaby, E.H. Esmail, E. Fahmy, Corticobasal degeneration: clinical characteristics and multidisciplinary therapeutic approach in 26 patients, Neurol. Sci. 36 (2015) 1651–1657, https://doi.org/10.1007/s10072-015-2226-x.