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.

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.

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] (Figure1). 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, 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 between 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.

EPIDEMIOLOGY AND CLINICAL PHENOMENOLOGY

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] (Figure 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 degrees 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] (Video 1). 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] (Figure 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] (Video 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] (Video 3). 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] (Figure 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] (Figure 1, lower panel: B). Hemi-dystonia may present early in 11% of PSP cases, even before the onset of the typical oculomotor abnormalities, suggesting a clinical diagnosis of CBS [33].

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] (Figure 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].

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 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].

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,~~59~~ 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 [61]. 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,~~65~~ 66]. Alternative mechanisms may include the loss of inhibitory interneurons in the cortex or thalamus, as demonstrated in PSP [6,67,68]. Another neurophysiological 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.

DIAGNOSTIC CLUES

The recognition of specific dystonic features, including their prevalence, topographic distribution, and relationship with dopaminergic therapy, may all assist in distinguishing between different APD or between APD and PD. In general, dystonia is overall more frequent in APD than PD; in particular blepharospasm and anterocollis are 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].

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.

TREATMENT

Therapeutic strategies for dystonia in APD consist of both pharmacological and non-pharmacological approaches (Figure 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].

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.

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FIGURE LEGENDS

Figure 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).

Figure 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.

VIDEO LEGENDS

Video 1. Diurnal and nocturnal stridor in a patient with multiple system atrophy.

Video 2. Striatal toe in a patient with progressive supranuclear palsy (note also the prominent vertical gaze palsy).

Video 3. Apraxia of eyelid opening in a patient with progressive supranuclear palsy.

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*	20/35 (67%)	OPCA/SND	Retrospective chart review	35	[16] Wenning et al., 1995
Facial dystonia*	5/12 (42%)	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
Orofacial dystonia	17/67 (25%)	MSA-P	Cross-sectional (Follow-up in 17)	NA	[11] Kollensperger et al., 2008
Facial dyskinesia*	25/100 (25%)	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
Craniofacial dystonia	31/191 (16%) (3*/31)	MSA	Prospective, 5 y follow-up	NA	[5] Yoon, 2018
Cervical*	7/12 (58%)	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
Cervical	6/24 (25%)	MSA-P/MSA-C	Prospective follow-up	5	[10] Boesch et al., 2002
Cervical	5/191 (2%) (1*/5)	MSA	Prospective follow-up	NA	[5] Yoon, 2018
Anterocollis	8/19 (42%)	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Anterocollis	25/67 (37%)	MSA-P	Cross-sectional (Follow-up in 17)	NA	[11] Kollensperger et al., 2008
Anterocollis	2/23 (8%)	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
Anterocollis	9/100 (9%)	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
Anterocollis	3/35 (8%)	OPCA/SND	Retrospective chart review	35	[16] Wenning et al., 1995
Anterocollis / Torticollis	3/140 (2%)	OPCA/ SND	Literature review	140	[7] Rivest et al., 1990
Retrocollis	1/23 (4%)	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
Limb dyskinesia*	53/100 (53%)	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
Limb dyskinesia*	3/12 (25%)	MSA-P	Prospective follow-up	5	[10] Boesch et al., 2002
Striatal hand deformities	5/19 (26%)	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Limb	5/24 (20%)	MSA-P/MSA-C	Prospective follow-up	5	[10] Boesch et al., 2002
Contractures of hands/feet	10/67 (15%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Limb	3/23 (13%)	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
Limb	2/191 (1%) (*/2)	MSA	Prospective, follow-up	NA	[5] Yoon, 2018
Limb	1/140 (0.7%)	SND	Literature review	140	[7] Rivest et al., 1990
Laryngeal	33/67 (49%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Nocturnal stridor	25/67 (37%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Stridor	34/100 (34%)	OPCA/SND	Retrospective chart review	100	[15] Wenning et al., 1994
Stridor	12/35 (34%)	OPCA/SND	Retrospective chart review	35	[16] Wenning et al., 1995
Nocturnal stridor	19/73 (26%)	MSA-P	Multicenter Cross-sectional	NA	[18] Moreno-Lopez, 2011
Diurnal stridor	15/67 (22%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Nocturnal stridor	2/13 (15%)	MSA-C	Multicenter Cross-sectional	NA	[18] Moreno-Lopez, 2011
Laryngeal	1/140 (0.7%)	OPCA	Literature review	140	[7] Rivest et al., 1990
Camptocormia	21/67 (31%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Trunk	5/19 (26%)	MSA	Retrospective chart review	NA	[13] Ashour & Jankovic, 2006
Camptocormia	1/23 (4%)	MSA	Retrospective chart review	NA	[12] Godeiro-Junior, 2008
Pisa syndrome	15/67 (2%)	MSA-P	Cross-sectional	NA	[11] Kollensperger et al., 2008
Trunk	2/191 (1%) (0*/2)	MSA	Prospective follow-up	NA	[5] Yoon, 2018
Trunk	1/140 (0.7%)	SND	Literature review	140	[7] Rivest et al., 1990

MSA, multiple system atrophy; MSA-P, parkinsonian subtype; MSA-C, cerebellar subtype; OPCA, olivopontocerebellar atrophy; SND, striatonigral degeneration; 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 [106,107]; whereas all the studies conducted after 1998 are based on the criteria provided by Gilman et al., 1998 [108].

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
Limb	(26%) 22/83 9/22 hemi dystonia	PSP	Retrospective chart review	NA	[33] Barclay & Lang, 1997
	(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 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].

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].

Figure 1.

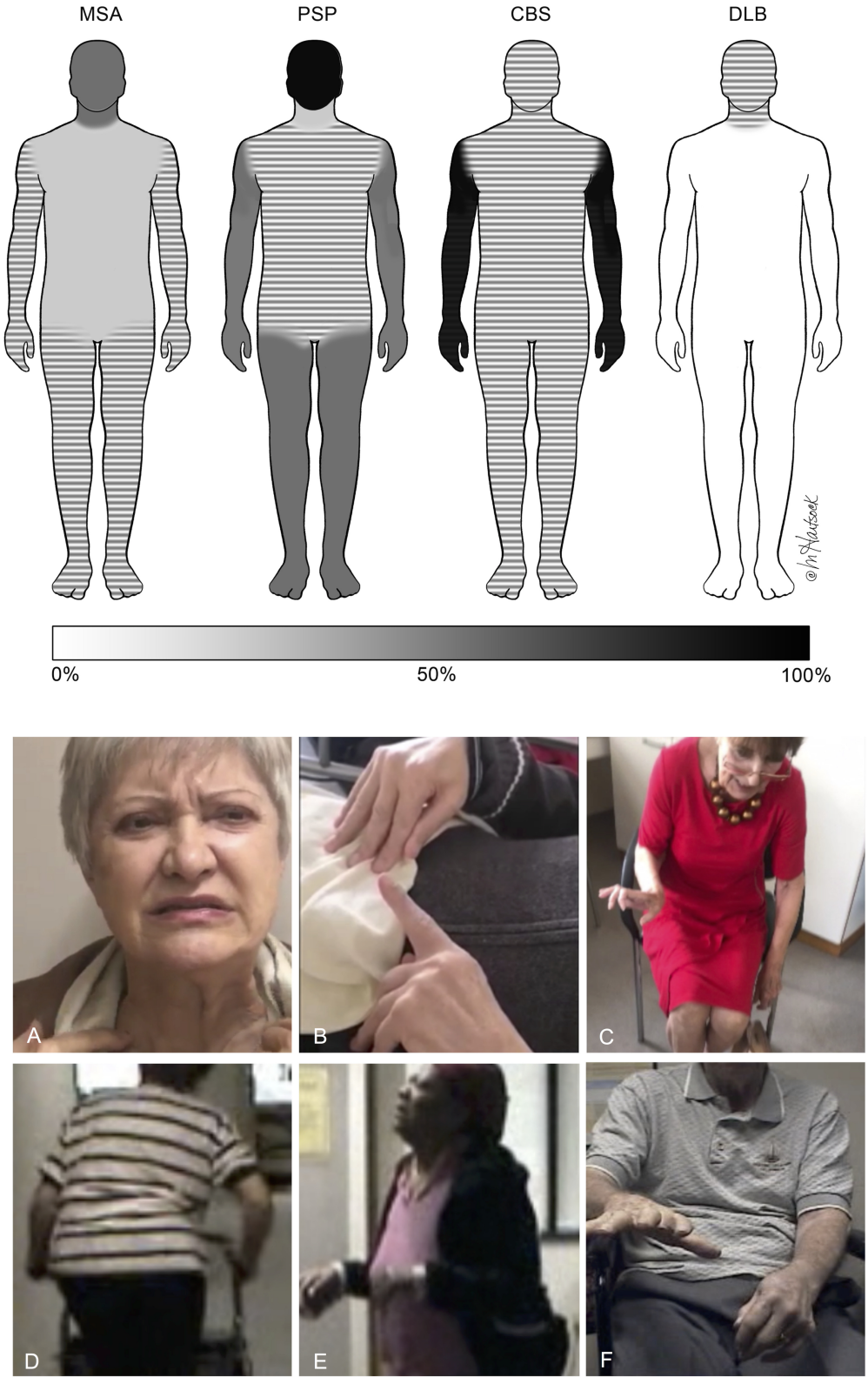
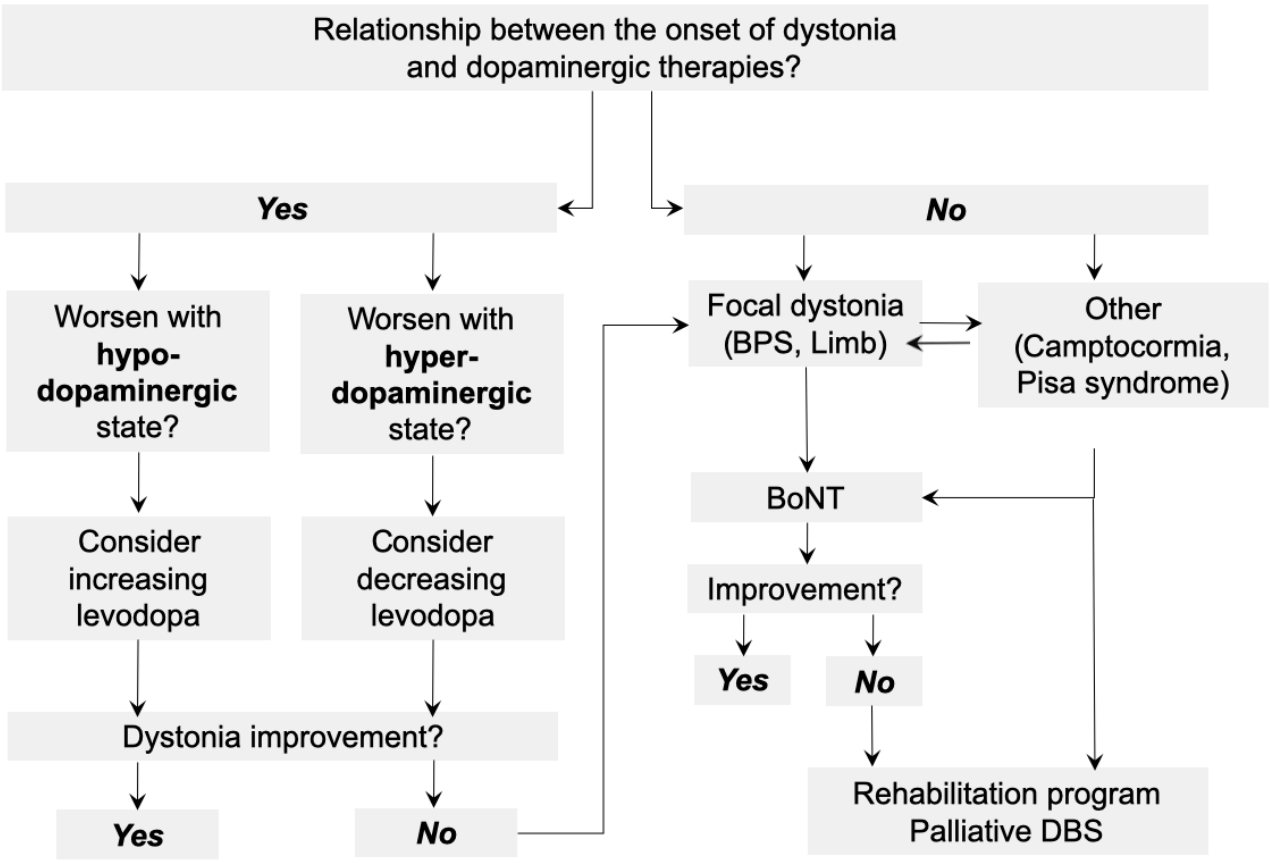


Figure 2.


Relationship between the onset of dystonia and dopaminergic therapies?
Yes
No
Worsen with hypo-dopaminergic state?
Worsen with hyper-dopaminergic state?
Consider increasing levodopa
Consider decreasing levodopa
Dystonia improvement?
Yes
No
Focal dystonia (BPS, Limb)
Other (Camptocormia, Pisa syndrome)
BoNT
Improvement?
Yes
No
Rehabilitation program
Palliative DBS