

35

Dystonia in Parkinsonian Syndromes

Alberto Albanese

Instituto Nazionale Neurologico Carlo Besta, Università Cattolica del Sacro Cuore, Milano, Italy

It has long been assumed, with clinical observations dating back more to a century, that dystonia is an integral part of Parkinson's disease (PD) (1).

Dystonia associated with parkinsonism may also occur in various hereditary conditions involving the basal ganglia, such as Wilson's disease (2); Huntington's disease (3); Hallervorden-Spatz syndrome (4); corticobasal ganglionic degeneration (CBGD) (5); or progressive supranuclear palsy (6,7). Dystonia and parkinsonian signs are also key features of dopa-responsive dystonia (8); X-linked dystonia-parkinsonism (9); rapid-onset dystonia-parkinsonism (10,11); and hemiparkinsonian-hemiatrophy syndrome (12,13). Although dystonia and parkinsonism are commonly associated, their relationship is far from being understood. The main impediment for creating pathophysiological links between dystonia and the different parkinsonian syndromes has been the lack of diagnostic tests and the paucity of clinicopathological reports (6). The differential diagnosis of parkinsonian syndromes has been greatly improved in recent years, mainly after the introduction of validated diagnostic criteria and laboratory examinations, particularly genetic testing and brain imaging.

CLINICAL FEATURES OF DYSTONIA

Dystonia is currently defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or

abnormal postures (14). This movement disorder is associated with a defect of cortical inhibition, resulting in inaccurate selection of movements, as well as with a disordered preparation for movement, resulting in inappropriate processing of sensory stimuli (15).

The most typical presentation is torsion dystonia, encompassing a combination of dystonic movements and dystonic postures (16,17). Dystonic movements have a twisting nature and a directional quality and are consistent and predictable (18). Dystonic postures are associated with a sensation of rigidity and traction and are primarily responsible for pain. In torsion dystonia patients, postures may appear some months or few years before dystonic movements are seen; the combination of these two clinical signs is a key feature for the clinical diagnosis of torsion dystonia. Fixed dystonia is the syndrome of dystonic postures without dystonic movements. As opposed to mobile (or torsion) dystonia, fixed dystonia is often secondary to other neurological disorders.

Dystonic movements and postures may be alleviated by a number of specific voluntary movements, which have been called "sensory tricks" or "*gestes antagonistes*" (19,20). They are thought to inhibit, at the central level, the cortical overflow that causes dystonia (21). Their finding is a clinical sign for the diagnosis of dystonia. Voluntary movements, particularly purposeful skilled actions, commonly aggravate dystonia, either mobile or fixed. Dystonic camptocormia is a focal form of

fixed dystonia that is induced or aggravated by walking (22) and is typically relieved by the *geste antagoniste* of straightening the trunk by pushing against a cane or a wall. Dystonic camptocormia is occasionally reported as a primary disorder of the elderly and is commonly observed in PD.

CONTRACTURES IN PARKINSONIAN SYNDROMES

Deformities or contractures of the hands, and sometimes the feet, were recognized to occur in some parkinsonian patients in the pre-levodopa era. Charcot (23) pointed out that they were not dissimilar to those of rheumatoid arthritis, except that there was no swelling or stiffness in the joints. Similar observations were performed in the pre-levodopa era on clinically typical PD cases (24). It is difficult to be certain whether the cases described had idiopathic PD or other parkinsonian syndromes, such as post-encephalitic parkinsonism (25) or parkinsonism-dementia complex (26,27). Some of these hand deformities may have been due to contraction, rather than contracture because it has been observed that they could be corrected by stereotactic thalamotomy in severe cases of parkinsonism (28). The term contractures has also been occasionally used to indicate a fixed posture or deformity occurring in parkinson-

ian patients, some of whom have received a postmortem diagnosis of multiple system atrophy (MSA) (29–31). Therefore, the issue of whether contractures occurring in different parkinsonian syndromes have distinctive features has remained unsettled.

It is not established whether such contractures represent the consequence of longstanding fixed dystonic posturing (32) or whether they constitute a different pathophysiological entity. Several mechanisms are probably involved. Dystonia affecting the hands, either due to the disease itself or more commonly to drug use, gives rise to a slight ulnar deviation of the fingers, flexion of the metacarpophalangeal joint, and hyperextension of the interphalangeal joints (Fig. 35.1) (33). These deformities are initially intermittent and can be related to the timing of drugs but later become clenched-fist contractures. It is thought that hyperactivity of the small muscles of the hands is an important contributing factor in producing hand deformities in PD. It has been shown that blocking the ulnar nerve at the elbow with local anesthetic can reverse finger flexion deformities, whereas stimulation of the same nerve in normal hands can produce finger deformities similar to those observed in PD (28). The posture adopted by the patient, especially in cases with severe rigidity, also seems to be a contributing factor. The occurrence of hand deformities is related to the



FIGURE 35.1. This patient with clinically typical Parkinson's disease dating for more than 10 years developed a fixed contracture of the left hand.

degree of muscular rigidity and is unrelated to the extent or duration of tremor (29).

The principal cause of contractures is a shortening of the length of muscle fibers due to a reduced number of sarcomeres, precipitated by prolonged immobilization of the muscles at short lengths during sustained muscle contraction. Additionally, changes in the physical properties (plasticity and viscoelasticity) of muscles, tendon, joint, and surrounding soft tissue occur, leading to atrophy and fibrosis (34). Contractures can develop quite rapidly and usually within 12 months (32).

The question of whether contractures represent an extremely severe form of fixed dystonia is also unsettled. Unlike fixed dystonia, contractures are not alleviated by *gestes antagonistes* and are not aggravated by performing voluntary or skilled movements.

DYSTONIA IN PARKINSON'S DISEASE

Dystonic manifestations now encountered in patients with PD are usually related to anti-parkinsonian treatment. Dystonic foot response was recognized as an early parkinsonian feature well before the discovery of levodopa (1). Similar observations were performed in levodopa-treated patients, who developed "off"-related early morning foot dystonia after overnight medication withdrawal (35) or daytime foot dystonia (36). Dystonia is the most common early morning dyskinesia occurring in patients with PD (37). It has been readily established that dopaminergic medication could reverse foot dystonia in patients with PD (38). Attempts to correlate dystonia with plasma levodopa concentrations yielded inconsistent results (39,40), indicating that dystonia is not simply related to the pharmacokinetics of levodopa.

The distinction between dyskinesias occurring when adequate mobility is warranted by dopaminergic medication ("on" period) and those occurring in the "off" period (when medication has been withdrawn) provides the basis for the current classification. Because different forms of dystonia could be observed

in the "on" and the "off" periods, the question has arisen about whether distinctive clinical features can be documented. Several forms of "off"-related dystonia (pretreatment, early morning, and "off"-period dystonia) have been recognized (41).

"Off"-period dystonia is the most common type of dystonia seen in PD. It is an often painful fixed dystonia occurring in the "off" periods, mainly affecting the limbs. Foot dystonia is the most common form. Typical "off"-period foot dystonia involves plantarflexion and inversion of the ankle, together with plantarflexion of the toes except for the big toe, which is frequently extended. Voluntary movement often aggravates fixed dystonia in PD, whereas action-foot dystonia may lead to recurrent spasms (38). Contractures, instead, often occur in the upper limb and are not aggravated by voluntary movement.

Although "on"-period dyskinesias were originally described as choreoathetoid (42), as opposed to pure dystonia in the "off" state, they are in fact choreodystonic. Mobile dystonia is commonly combined with chorea (or sometimes a different dyskinesia) in the "on" periods (43).

Interestingly, mobile dystonia has never been reported in PD "off" periods.

Clinical Features of "Off"-period Dystonia in PD

Charcot (23) was the first to draw attention to early dystonic foot posturing, and Purves-Stewart (1), a few years later, recognized similar foot posturing in five of his 28 cases. Numerous authors have since emphasized this clinical feature, making it the most common dystonic manifestation in untreated patients with alleged PD (36,41,44-46). Foot dystonia is often painful, it commonly occurs in the "off" period and may lead to "dystonic claudication" (38). Upper limb dystonia has also been recognized in classic (47) and more recent (36,41,44-46) descriptions of patients with PD.

Approximately one quarter to one third of the patients managed before the levodopa era may

have eventually developed hand and foot dystonia (33). A wide variety of dystonic manifestations have recently been associated with PD, either coincident with its onset or up to 25 years before (49). These include cranial dystonia (44,45,48,49); cervical dystonia (44,45,48,49); axial dystonia with scoliosis (46,48); and various dystonic movement and posturing of both upper and lower limb, most often ipsilateral to the side most affected by parkinsonism (44–46, 48,49). Unilateral parkinsonism has also been observed in association with hemidystonia of the same body side (44–46,49).

Dystonia at disease onset and a progressive parkinsonism, with sustained response to low doses of levodopa and occurrence of “on”-period dyskinesias, is the classic presentation in patients with mutations of the parkin (*PARK2*) gene (50,51). Patients linking to the *PARK7* locus also present dystonia (52), but interestingly, dystonia is very rarely observed in patients linking to the *PARK6* locus (53). These data may indicate that genetic susceptibility to dystonia varies in different parkinsonian forms.

“Off”-period dystonia is more common than usually appreciated; increased blink rate in patients with PD may reveal “off”-period blepharospasm (54). A special focal form of “off”-period dystonia is the paradoxical contraction of the puborectalis muscle during straining for defecation, characterized by excessive recruitment of synergistic and antagonistic muscle groups during voluntary activity and lack of reciprocal inhibition (55). It has been observed that apomorphine can reverse acute constipation occurring as an “off”-related phenomenon soon after withdrawal of levodopa in patients with PD (56) and that this drug specifically improves anorectal dysfunction in PD (57). In our series, we observed that 13% of 120 patients with PD and chronic constipation could not defecate due to paradoxical puborectalis contraction at straining (58).

Clinical Features of “On”-period Dystonia in PD

In the first reports of chronic levodopa therapy, dyskinesias were recognized as a

complication (59–64). It has been observed that the clinical features of levodopa-induced dyskinesias vary with the clinical fluctuation of parkinsonism, and that they possibly reflect changes of plasma concentrations of levodopa (65). Some descriptions of “on”-period dyskinesias have associated the time of dyskinesia onset with the motor improvement caused by levodopa (hence, levodopa-induced dyskinesia) and have described their clinical appearance (i.e., chorea, dystonia, myoclonus, and so on) (59,66). “On”-period dyskinesias are evidently related to the short-duration response to levodopa, starting from 15 minutes to 1 hour after a dose and disappearing after 1 to 3 hours (67). They can also be observed in relation to the short-duration response after the administration of dopamine agonists or as an aftermath of combined therapy in those patients taking multiple medications. “On”-period dyskinesias are not dependent on plasma levodopa concentrations (39,40), and the distinction between monophasic (or peak-dose) and biphasic (or beginning-of-dose and end-of-dose) dyskinesias is probably artificial (68). Dyskinesias related to medication have different clinical features from those induced by high-frequency stimulation of the subthalamic nucleus (69,70).

The most common clinical presentation of “on”-period dyskinesias is a combination of chorea and dystonia (43). In the earliest descriptions of levodopa-induced dyskinesias, their complex phenomenology was clearly recognized (59). A classic report on the pattern of “on”-period dyskinesias induced by levodopa clearly emphasized their dystonic nature (67), whereas more recent observations have reckoned that “on”-period dyskinesias are choreic in 70% of patients (71). In our experience, dystonic features are almost invariably present when dyskinesias affect the limbs, whereas isolated chorea is observed in dyskinesias of the face. Monophasic dyskinesias commonly present a combination of dystonia and chorea, whereas biphasic (beginning-of-dose and end-of-dose dyskinesias) mainly have dystonic features (Fig. 35.2). “On”-period chorea occurring in PD has the

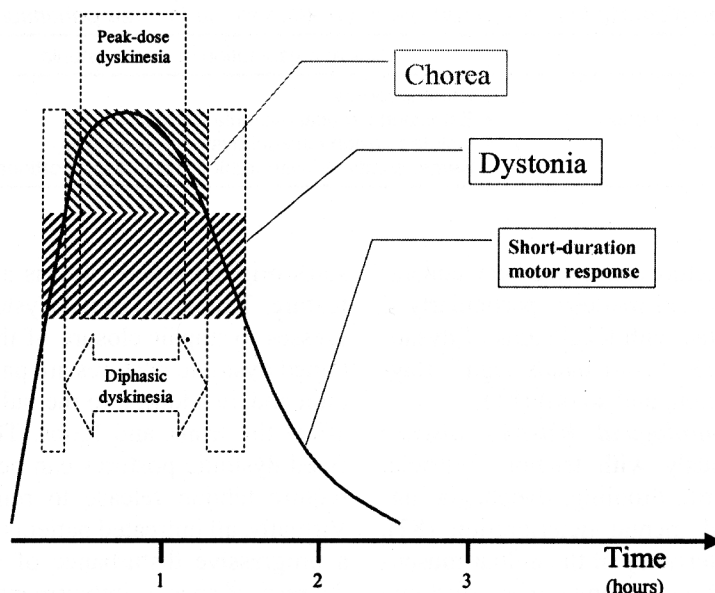


FIGURE 35.2. The clinical presentation of peak-dose dyskinesia is usually of a mixed type, choreic and dystonic, whereas diphasic dyskinesias are usually prevalently dystonic. This figure shows the time course of dystonia and chorea with reference to the short-duration motor response after a single acute administration of levodopa.

same neurophysiological features of degenerative chorea (72).

DYSTONIA IN PARKINSONIAN SYNDROMES

Although dystonia may occur in almost any of the parkinsonian syndromes, some have a particular tendency to associate with dystonia.

Degenerative Diseases with Parkinsonism and Dystonia

Nearly all reports of *CBGD* mention the presence of dystonia, but detailed characterization of the dystonic features is lacking (5,73,74). In a series of 66 patients with possible *CBGD*, 39 (59%) had dystonia (74). Of the four cases in this series who received a pathological confirmation of the diagnosis, three had dystonia during the course of the illness. Limb dystonia is the most common feature. Early asymmetrical limb dystonia commonly proceeds to fixed dystonic posturing

(75). Typically, the arm is adducted at the shoulder, the elbows and wrists flexed, and the arm extending in front or behind the body. Axial dystonia is a less common feature (76).

A progressive nuchal dystonia leading to a permanent contracture was reported in the first description of *progressive supranuclear palsy* (7). Focal or segmental dystonia, for example, in the form of limb dystonia or blepharospasm is not uncommon (6,77,78). With disease progression, cranial and cervical dystonia lead to a progressive contracture that contracts the mandible to close the mouth and the neck into a characteristic extended posture. Contractures of the hands are not uncommon (Table 35.1).

Mobile dystonia is uncommon in *MSA*, although contractures and fixed dystonia have been reported as prominent features (79). The paradigmatic form of fixed dystonia in *MSA* is antecollis or head-drop not associated to trunk flexion or camptocormia (80). Figure 35.3 depicts a patient with severe fixed axial dystonia associated with a unilateral clenched

TABLE 35.1. Paradigmatic features of “off”-period axial dystonia in three parkinsonian syndromes

Disease	Clinical presentation of axial dystonia
Parkinson's disease	• Camptocormia
Progressive supranuclear palsy	• Extension cervical dystonia (retrocollis)
Multiple system atrophy	• Isolated flexion cervical dystonia (antecollis)
	• Same, combined with trunk flexion (disproportionate antecollis)

fist. Hand contractures have also been considered specific clinical markers, particularly if they are associated with local signs of dysautonomia (so-called “cold hands sign,” Raynaud's phenomenon, and so on) (81).

Typically, *neurological Wilson's disease* presents insidiously with tremor, dystonia, rigidity, dysarthria, drooling, dysphagia, unsteady gait, and mental deterioration (82). Dystonia in the territory of the bulbar musculature is prominent; in one series, dystonia was more common than tremor as the initial feature (83). Cranial dystonia and pharyngeal dysmotility can be observed during the early disease stages (84). It may present as facial grimacing, blepharospasm, or lingual dystonia (85). A fixed “sardonic” smile with retracted lips and opened jaw, illustrated in Wil-

son's original report (82), is a highly typical feature. This fixed facial dystonia often progresses to impair closure of the mouth. Sustained dystonic postures are particularly common and, in addition to the bulbar region, can affect the trunk and limbs. The intensity of fixed dystonic postures can be so great as to require tendon release to relieve disability. Virtually, all untreated patients are affected by a progressive disturbance of speech. Lesser degrees of speech impairment include whispering dysphonia (86) and a characteristic inspiratory laugh, which “once heard is never forgotten” (87).

Post-encephalitic parkinsonism. In patients with encephalitis lethargica, various movement disorders were encountered during the acute encephalitic stage or during the post-en-

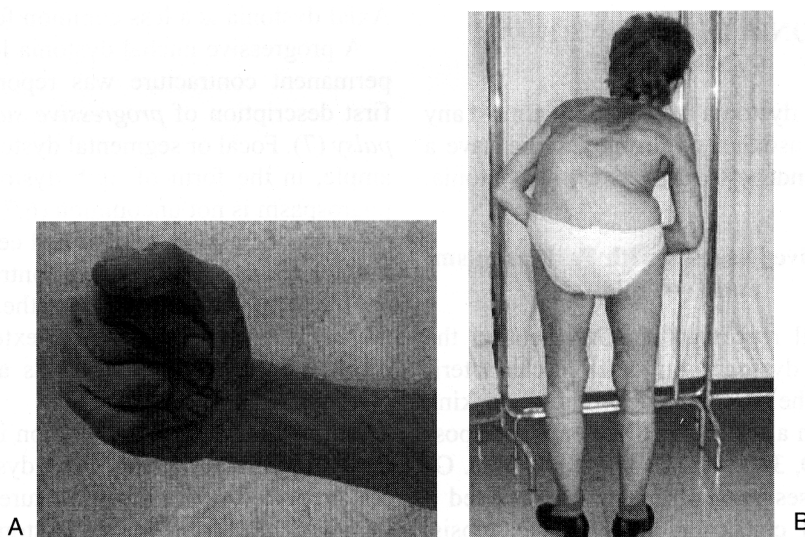


FIGURE 35.3. This patient has a 5-year history of multiple system atrophy and first developed a mobile dystonia of the right hand, in combination with a typical parkinsonian picture. **A:** The hand gradually turned into a fixed clenched fist. **B:** Camptocormia is associated with kyphosis and scoliosis of the spine.

cephalitic phase with or without parkinsonism (88–90). Dystonia was rarely described in post-encephalitic parkinsonism and usually had a cervical topography (90). It is likely that dystonia was largely unrecognized in the early reports if in a series of historical video segments on six post-encephalitic parkinsonism, five of the patients had dystonia (91).

Rapid-onset dystonia-parkinsonism is a rare autosomal-dominant movement disorder linked to chromosome 19q13 that is characterized by sudden onset of persistent primarily bulbar and upper limb dystonia and parkinsonism, generally during adolescence or early adulthood (10,92). Mild limb dystonia may occur years before the abrupt onset of combined dystonia-parkinsonism (93).

Different clinical types of *Hallervorden-Spatz syndrome* can be distinguished based on severity and age at disease onset. In early onset childhood types, the diagnosis is evident before 10 years of age; a rapidly progressive and a slowly progressive form have been described. In late-onset type, the diagnosis is evident after 10 years and before 18 years of age; it usually progresses slowly. The adult type of Hallervorden-Spatz syndrome also progresses slowly. In the early onset type, the motor disorder is characterized by dystonic postures, muscular rigidity, involuntary movements of choreoathetoid or tremulous type, and findings suggesting corticospinal tract dysfunction. Mental changes are indicative of dementia. The course, relentless and progressive, extends over several years, leading to death in early adulthood (94). The gene has been localized and recently identified (95).

Dopa-responsive dystonia is another genetic disorder associated with mutations of the guanosine triphosphate-cyclohydroxylase I gene on chromosome 14q (96). The classical phenotype presents in infancy or adolescence with postural abnormalities in the legs. Symptoms most often occur while walking and falls are common. Diurnal fluctuation of dystonia may be present, particularly in the form of "sleep benefit" (8), but because this is reported in 50% to 60% of cases, such an observation is not necessary for the diagnosis.

Response to levodopa is sustained and dramatic; generalization occurs in untreated patients from 1 to 12 years after onset (97). Parkinsonian features usually occur later than dystonia; less common forms present at a later age with parkinsonian features (98). In a series of 86 patients, the following clinical features were reported as most common (99): abnormal gait, focal limb dystonia, scoliosis, rest or postural tremor, bradykinesia, rigidity, and diurnal fluctuations.

X-linked dystonia-parkinsonism (Lubag) is a rare disorder that mainly affects males of Filipino origin (9). Age at onset varies from adolescence to middle age; progression is to generalization. The patients have dystonia and associated parkinsonian signs in about one third of cases.

CONCLUSIONS

In conclusion, the number of diseases and syndromes in which parkinsonian features are associated with dystonia is so impressively high to impose the existence of links between these two conditions. Such links have not been fully elucidated. Efficacious symptomatic treatments only exist for PD, so a distinction between "on" and "off" periods is meaningless in other parkinsonian syndromes. However, it seems clear that "on"-period and "off"-period dystonia have different features in PD: Mobile dystonia occurs in the "on" period (when it is often combined with chorea), but not in the "off" period; the opposite is true for fixed dystonia. Untreatable parkinsonian syndromes must be compared to the "off" period in PD; still mobile dystonia is commonly observed in untreated parkinsonian syndromes (Table 35.2). This marks a clear difference with PD. Contractures occur in the "off" period in PD and in other parkinsonian syndromes; however, there are no clinical distinctive features.

The topography of dystonia is also a relevant clinical feature. It is proposed that orofacial and limb dystonia may be generated through different pathophysiological mechanisms. Limb or axial dystonia (which is a fea-

TABLE 35.2. Presentation of different forms of dystonia in Parkinson's diseases compared with other parkinsonian syndromes

Clinical feature	Parkinson's disease		Other parkinsonian syndromes	
	Off period	On period	Off period	On period ^a
Contractures	+	—	++	NA
Fixed dystonia	+++	—	++	NA
Mobile (torsion) dystonia	—	+++ ^b	+++	—

Note: +, it may occur; ++, occurs often; +++, occurs very often; —, does not occur; NA, not available.

^aOn-period dystonia occurs in some, but not all, patients with a parkinsonian syndrome other than Parkinson's disease.

^bIt is often combined with chorea.

ture of a PD "off" period, of dopa-responsive dystonia, and others) may be caused by a state of reduced dopaminergic transmission. Oro-facial dystonia (as observed in Hallervorden-Spatz syndrome) may be caused by pallidal dysfunction. Finally, combined forms may have a combined pathophysiology.

REFERENCES

- Purves-Stewart J. Paralysis agitans with an account of a new symptom. *Lancet* 1898; 2:1258–1260.
- Sternlieb I, Giblin DR, Scheinberg H. Wilson's disease. In: Marsden CD, Fahn S, eds. *Movement disorders*, 2nd ed. London: Butterworth, 1987:288–302.
- Shoulson I. Huntington's disease. A decade of progress. *Neurol Clin* 1984;2:515–526.
- Mourelatos Z, Golden JA. 24 year old female with progressive lower extremity dystonia, dysarthria, dysphagia and mental impairment. *Brain Pathol* 2000;10:171–172.
- Frucht S, Fahn S, Chin S, et al. Levodopa-induced dyskinesias in autopsy-proven cortical-basal ganglionic degeneration. *Mov Disord* 2000;15:340–343.
- Rivest J, Quinn N, Marsden CD. Dystonia in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Neurology* 1990;40:1571–1578.
- Steele JC, Richardson JC, Olszewski J. 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* 1964;10:333–358.
- Segawa M, Hosaka A, Miyagawa F, et al. Hereditary progressive dystonia with marked diurnal fluctuation. In: Eldridge R, Fahn S, eds. *Dystonia*. New York: Raven Press, 1976:215–233.
- Wilhelmsen KC, Weeks DE, Nygaard TG, et al. Genetic mapping of "lubag" (X-linked dystonia-parkinsonism) in a Filipino kindred to the pericentromeric region of the X chromosome. *Ann Neurol* 1991;29:124–131.
- Dobyns WB, Ozelius LJ, Kramer PL, et al. Rapid-onset dystonia-parkinsonism. *Neurology* 1993;43:2596–2602.
- Brashear A, Butler IJ, Hyland K, et al. Cerebrospinal fluid homovanillic acid levels in rapid-onset dystonia-parkinsonism. *Ann Neurol* 1998;43:521–526.
- Greene PE, Bressman SB, Ford B, et al. Parkinsonism, dystonia, and hemiatrophy. *Mov Disord* 2000;15:537–541.
- Nygaard TG, Duvoisin RG. Hereditary dystonia-parkinsonism syndrome of juvenile onset. *Neurology* 1986;36:1424–1428.
- Fahn S, Marsden CD, Calne DB. Classification and investigation of dystonia. In: Marsden CD, Fahn S, eds. *Movement disorders*, 2nd ed. London: Butterworth, 1987:332–358.
- Hallett M. Disorder of movement preparation in dystonia. *Brain* 2000;123:1765–1766.
- Albanese A. *I gangli motori e i disturbi del movimento*. *Neurobiologia clinica*. Padova: Piccin, 1991.
- Ghika J, Albanese A. Dyskinesias. In: Fisher RS, Bogousslavsky J, eds. *Textbook of neurology*. Boston: Butterworth-Heinemann, 1998:247–254.
- Bressman SB. Dystonia. *Curr Opin Neurol* 1998;11:363–372.
- Gomez-Wong E, Marti MJ, Cossu G, et al. The "geste antagonistique" induces transient modulation of the blink reflex in human patients with blepharospasm. *Neurosci Lett* 1998;251:125–128.
- Greene PE, Bressman S. Exteroceptive and interoceptive stimuli in dystonia. *Mov Disord* 1998;13:549–551.
- Hallett M. Is dystonia a sensory disorder? *Ann Neurol* 1995;38:139–140.
- Djaldetti R, Mosberg-Galili R, Sroka H, et al. Camptocormia (bent spine) in patients with Parkinson's disease—characterization and possible pathogenesis of an unusual phenomenon. *Mov Disord* 1999;14:443–447.
- Charcot JM. *Leçons sur les maladies du système nerveux*. Paris: A. Delahaye, 1872.
- Reynolds F, Petropoulos G. Hand deformities in parkinsonism. *J Chronic Dis* 1965;18:593–595.
- Martin JP. *The basal ganglia and posture*. London: Pitman, 1967.
- Chan KM, Tsuji S, Gajdusek DC, et al. Studies on the natural history of parkinsonism-dementia of Guam, II: motor neuron involvement and postural deformities in advanced age. *Neurology* 1979;29:578.
- Chen K-M, Chase TN. Parkinsonism-dementia. In: Vinken PJ, Bruyn GW, Klawans HL, eds. *Extrapyramidal disorders*. Amsterdam: Elsevier Science, 1986:167–173.
- Gortvai P. Deformities of the hands and feet in parkinsonism and their reversibility by operation. *J Neurol Neurosurg Psychiatry* 1963;26:33–36.
- Quinn NP, Ring H, Honavar M, et al. Contractures of

- the extremities in parkinsonian subjects: a report of three cases with a possible association with bromocriptine treatment. *Clin Neuropharmacol* 1988;11:268-277.
30. Thomas A. Atrophie du cerveau et sclérose en plaques. *Rev Neurol Paris* 1903;3:121-131.
 31. Trotter JL. Striatonigral degeneration: Alzheimer's disease and inflammatory changes. *Neurology* 1973;23:1211-1216.
 32. Kyriakides T, Hewer RL. Hand contractures in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:1221-1223.
 33. Marsden CD, Parkes JD, Quinn N. Fluctuations of disability in Parkinson's disease. Clinical aspects. In: Marsden CD, Fahn S, eds. *Movement disorders*. London: Butterworth, 1981:96-122.
 34. O'Dwyer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. *Brain* 1996;119:1737-1749.
 35. Melamed E. Early-morning dystonia: a late side effect of long term levodopa therapy in Parkinson's disease. *Arch Neurol* 1979;36:308-310.
 36. Nausieda PA, Weiner WJ, Klawans HL. Dystonic foot response of parkinsonism. *Arch Neurol* 1980;37:132-136.
 37. Cubo E, Gracies JM, Benabou R, et al. Early morning "off" medication dyskinesias, dystonia, and choreic subtypes. *Arch Neurol* 2001;58:1379-1382.
 38. Poewe W, Lees AJ, Stieger D, et al. Foot dystonia in Parkinson's disease: clinical phenomenology and neuropharmacology. *Adv Neurol* 1986;45:357-360.
 39. McHale DM, Sage JI, Sonsalla PK, et al. Complex dystonia of Parkinson's disease: clinical features and relation to plasma levodopa profile. *Clin Neuropharmacol* 1990;13:164-170.
 40. Zimmerman TR Jr, Sage JI, Lang AE, et al. Severe evening dyskinesias in advanced Parkinson's disease: clinical description, relation to plasma levodopa, and treatment. *Mov Disord* 1994;9:173-177.
 41. Kidron D, Melamed E. Forms of dystonia in patients with Parkinson's disease. *Neurology* 1987;37:1009-1011.
 42. Lees AJ, Shaw KM, Stern GM. "Off period" dystonia and "on period" choreoathetosis in levodopa-treated patients with Parkinson's disease. *Lancet* 1977;2:1034.
 43. Fahn S. The spectrum of levodopa-induced dyskinesias. *Ann Neurol* 2000;47[Suppl 1]:S2-S9.
 44. LeWitt PA, Burns RS, Newman RP. Dystonia in untreated parkinsonism. *Clin Neuropharmacol* 1986;9:293-297.
 45. Poewe WH, Lees AJ, Stern GM. Dystonia in Parkinson's disease: clinical and pharmacological features. *Ann Neurol* 1988;23:73-78.
 46. Quinn NP, Critchley P, Marsden CD. Young onset Parkinson's disease. *Mov Disord* 1987;2:73-91.
 47. Souques MA. Rapport sur les syndromes parkinsoniens. *Rev Neurol (Paris)* 1921;37:534-573.
 48. Katchen M, Duvoisin RC. Parkinsonism following dystonia in three patients. *Mov Disord* 1986;1:151-157.
 49. Klawans HL, Paleologos N. Dystonia-Parkinson syndrome: differential effects of levodopa and dopamine agonists. *Clin Neuropharmacol* 1986;9:298-302.
 50. Lucking CB, Durr A, Bonifati V, et al. Association between early-onset Parkinson's disease and mutations in the parkin gene. *N Engl J Med* 2000;342:1560-1567.
 51. Tassin J, Durr A, Bonnet AM, et al. Levodopa-responsive dystonia. GTP cyclohydrolase I or parkin mutations? *Brain* 2000;123:1112-1121.
 52. van Duijn CM, Dekker MC, Bonifati V, et al. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. *Am J Hum Genet* 2001;69:629-634.
 53. Valente EM, Bentivoglio AR, Dixon PH, et al. Localization of a novel locus for autosomal recessive early-onset parkinsonism, PARK6, on human chromosome 1p35-p36. *Am J Hum Genet* 2001;68:895-900.
 54. Kimber TE, Thompson PD. Increased blink rate in advanced Parkinson's disease: a form of "off"-period dystonia? *Mov Disord* 2000;15:982-985.
 55. Mathers SE, Kempster PA, Swash M, et al. Constipation and paradoxical puborectalis contraction in anismus and Parkinson's disease: a dystonic phenomenon? *J Neurol Neurosurg Psychiatry* 1988;51:1503-1507.
 56. Merello M, Leiguarda R. Adynamic bowel syndrome in Parkinson's disease with dramatic response to apomorphine. *Clin Neuropharmacol* 1994;17:574-577.
 57. Edwards LL, Quigley EM, Harned RK, et al. Defecatory function in Parkinson's disease: response to apomorphine. *Ann Neurol* 1993;33:490-493.
 58. Bentivoglio AR, Maria G, Brisinda G, et al. Outlet type constipation in patients with Parkinson's disease treated with botulinum toxin. *Mov Disord* 2000;15[Suppl 3]:124.
 59. Barbeau A. L-Dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Canad Med Assoc J* 1969;101:59-68.
 60. Barbeau A. Long-term side-effects of levodopa. *Lancet* 1971;1:395.
 61. Barbeau A. Diphasic dyskinesias during levodopa therapy. *Lancet* 1975;1:756.
 62. Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism. Chronic treatment with L-dopa. *N Engl J Med* 1969;280:337-345.
 63. Cotzias GC, van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 1967;276:374-379.
 64. Yahr MD, Duvoisin RC, Shear MJ, et al. Treatment of parkinsonism with levodopa. *Arch Neurol* 1969;21:343-354.
 65. Fahn S. Fluctuations of disability in Parkinson's disease: pathophysiology. In: Marsden CD, Fahn S, eds. *Movement disorders*. London: Butterworth, 1982:123-145.
 66. Duvoisin RC. Hyperkinetic reactions with L-dopa. *Current concepts in the treatment of parkinsonism*. New York: Raven Press, 1974:203-210.
 67. Muentner MD, Sharpless NS, Tyce GM, et al. Patterns of dystonia ('I-D-I' and 'D-I-D') in response to L-dopa therapy for Parkinson's disease. *Mayo Clin Proc* 1977;52:163-174.
 68. Marconi R, Lefebvre-Caparras D, Bonnet AM, et al. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord* 1994;9:2-12.
 69. Krack P, Pollak P, Limousin P, et al. From off-period dystonia to peak-dose chorea. The clinical spectrum of varying subthalamic nucleus activity. *Brain* 1999;122:1133-1146.
 70. Moro E, Scerrati M, Romito LM, et al. Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology* 1999;53:85-90.

71. Luquin MR, Scipioni O, Vaamonde J, et al. Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. *Mov Disord* 1992;7:117-124.
72. Hashimoto T, Shindo M, Yanagisawa N. Enhanced associated movements in the contralateral limbs elicited by brisk voluntary contraction in choreic disorders. *Clin Neurophysiol* 2001;112:1612-1617.
73. Greene PE, Fahn S, Lang AE, et al. What is it? Case 1, 1990: progressive unilateral rigidity, bradykinesia, tremulousness, and apraxia, leading to fixed postural deformity of the involved limb. *Mov Disord* 1990;5:341-351.
74. Vanek ZF, Jankovic J. Dystonia in corticobasal degeneration. *Adv Neurol* 2000;82:61-67.
75. Rinne JO, Lee MS, Thompson PD, et al. Corticobasal degeneration. A clinical study of 36 cases. *Brain* 1994;117:1183-1196.
76. Wenning GK, Litvan I, Jankovic J, et al. Natural history and survival of 14 patients with corticobasal degeneration confirmed at postmortem examination. *J Neurol Neurosurg Psychiatry* 1998;64:184-189.
77. Barclay CL, Lang AE. Dystonia in progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 1997;62:352-356.
78. Rafal R, Friedman J. Limb dystonia in progressive supranuclear palsy. *Neurology* 1987;37:1546-1549.
79. Quinn N. Multiple system atrophy. In: Marsden CD, Fahn S, eds. *Movement disorders*, 3rd ed. London: Butterworth-Heinemann, 1994:262-281.
80. Quinn NJ. Disproportionate antecollis in multiple system atrophy. *Lancet* 1989;1:844.
81. Klein C, Brown R, Wenning G, et al. The "cold hands sign" in multiple system atrophy. *Mov Disord* 1997;12:514-518.
82. Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. *Brain* 1912;34:295-309.
83. Starosta-Rubinstein S, Young AB, Kluin K, et al. Clinical assessment of 31 patients with Wilson's disease: correlations with structural changes on magnetic resonance imaging. *Arch Neurol* 1987;44:365-370.
84. Gulyas AE, Salazar-Grueso EF. Pharyngeal dysmotility in a patient with Wilson's disease. *Dysphagia* 1988;2:230-234.
85. Liao KK, Wang SJ, Kwang SY, et al. Tongue dyskinesia as an early manifestation of Wilson's disease. *Brain Dev* 1995;13:451-453.
86. Parker N. Hereditary whispering dysphonia. *J Neurol Neurosurg Psychiatry* 1985;48:218-224.
87. Walshe JM, Yealland M. Wilson's disease: the problem of delayed diagnosis. *J Neurol Neurosurg Psychiatry* 1992;55:692-696.
88. Doyle JB. Clinical manifestations and treatment of epidemic encephalitis. *Calif West Med* 1924;28:1-13.
89. Economo C. Encephalitis lethargica. *Wien Klin Wochenschr* 1917;30:581-585.
90. Economo C. *Die encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung*. Berlin: Urban & Schwarzenberg, 1929.
91. Evidente BK, Gwinn KA, Ceviness JN, et al. Early cinematographic cases of post-encephalitic parkinsonism and other movement disorders. *Mov Disord* 1998;13:167-169.
92. Kramer PL, Mineta M, Klein C, et al. Rapid-onset dystonia-parkinsonism: linkage to chromosome 19q13. *Ann Neurol* 1999;46:176-182.
93. Brashear A, Butler IJ, Ozelius LJ, et al. Rapid-onset dystonia-parkinsonism: a report of clinical, biochemical, and genetic studies in two families. *Adv Neurol* 1998;78:335-339.
94. Dooling EC, Schoene WC, Richardson EP. Hallervorden-Spatz syndrome. *Arch Neurol* 1974;30:70-83.
95. Zhou B, Westaway SK, Levinson B, et al. A novel pantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. *Nat Genet* 2001;28:345-349.
96. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. *Nat Genet* 1994;8:236-242.
97. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia. Long-term treatment response and prognosis. *Neurology* 1991;41:174-181.
98. Bandmann O, Marsden CD, Wood NW. Atypical presentations of dopa-responsive dystonia. *Adv Neurol* 1998;78:283-290.
99. Nygaard TG, Marsden CD, Duvoisin RC. Dopa-responsive dystonia. In: Fahn S, Marsden CD, Calne DB, eds. *Dystonia*, 2nd ed. New York: Raven Press, 1988:377-384.