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1. Introduction

Dystonia is a common feature in parkinsonian syndromes. In one Brazilian study, dystonia was observed in up to 50% of patients with “atypical parkinsonism” (1). It is also a prominent feature in various hereditary and neurodegenerative conditions implicating the basal ganglia such as Huntington’s disease, Wilson’s disease, familial basal ganglia calcifications and neurodegeneration with brain iron accumulation (NBIA) (2). Moreover, we have to keep in mind that a proportion of patients thought to have idiopathic Parkinson’s disease (PD) may later be found to have a different parkinsonian syndrome. In this chapter, the features of dystonia in parkinsonian syndromes will be discussed, with an emphasis on PD, progressive supranuclear palsy (PSP), multiple systems atrophy (MSA), with a brief discussion about other parkinsonian syndromes where dystonia can present. A general treatment algorithm is proposed for parkinsonian disorders that present with dystonia (see Figure 1).

2. Parkinson’s disease

The most common presentation of dystonia in PD is in the context of levodopa exposure, experienced by approximately 30% of patients (3-5). Several dystonic conditions exist: pre-treatment dystonia, peak dose dystonia, early morning dystonia and off period dystonia (3). Of which, the most common dystonic condition is off-state lower extremity painful dystonia (2,5). With regards to the area of involvement, Sheffield et al reported a frequency of 10% for facial dystonia, 10% for cervical, 30% for leg, 17.5% for arm and 7.5% for trunk dystonia (5). One common feature is that the dystonia is often ipsilateral to the initially affected (and therefore more affected) side in PD (2). The age of onset seems to be a major factor in the development of dystonia. It has been reported in up to 53%-60% of PD patients with onset before age 40 (2,5). As mentioned above we can classify the dystonic phenomenology in PD in relation to the exposure to levodopa: pre-treatment dystonia, peak dose dystonia, early morning dystonia and off period dystonia.

It was previously assumed that early onset primary torsion dystonia (PTD) and early onset PD shared common DYT1 gene mutations since both conditions seem to have dopamine dysfunction. However, a study have shown the association of DYT1 with early onset PTD but not early onset PD (6).
2.1 Pretreatment dystonia

This is generally defined as dystonia before exposure to levodopa. Kidron et al, reported the frequency of this type of dystonia to be 2.4% in their population (3). It typically involved the feet, was induced by volitional activity and usually involved the most parkinsonian side. Laryngeal dystonia has also been reported to precede the diagnosis of PD (7). This was effectively treated with botulinum toxin (BoNT) injections.

2.2 Peak dose dystonia

This is generally defined as dystonia occurring during the “on” period following levodopa dosing. Usually it is present in the midst of generalized dyskinesia, occurring in about 7% of patients (8). It appears mostly after long term exposure of levodopa. It affects mostly the extremities but it can also affect the trunk or the neck. Typically, it appears after 30 minutes to two hours of taking levodopa and stops after 15 minutes to 2 hours. It may not appear with every levodopa dose, nor does it have followed a particular pattern. The treatment is typically to decrease the dose of levodopa. However, PD symptoms may worsen with this approach. BoNT has been used effectively for treatment of this focal dystonia (5). Zolpidem has been reported to be effective in treating not only peak dose dystonia but also dyskinesia in PD patients (8), supposedly due to its GABA-ergic activity.

2.3 Early morning dystonia

This dystonia often appears upon awakening, before the first dose of levodopa, in up to 16% of patients (3,19). It also appears after long exposure to levodopa. It usually affects the lower extremities only, either unilaterally or bilaterally. This time, the most parkinsonian side is not always the affected side. It can happen when they still in bed or after trying to walk. It is mostly a painful dystonia lasting up to 2 hours. It usually subsides spontaneously without any relation to levodopa dosing. Changing or adding more levodopa may have little to no benefit in the treatment of this kind of dystonia. However, one study showed that adding baclofen the night prior, helped to shorten the duration of the dystonia in half of patients (3).

2.4 Off period dystonia

This type of dystonia develops when the benefits of levodopa on PD symptoms wears off. In one study, 10% was found to have off period dystonia (3). It can occur at rest or during activity, and it can be quite severe. In one case, the patient suffered a left metatarsal fracture in the setting of an off period dystonia (10). Also it appears after long exposure of levodopa. It has a tendency to appear ipsilaterally to the most parkinsonian side. In one study, off period dystonia appeared regardless of stopping levodopa abruptly or slowly. Dystonia appeared when the concentrations of levodopa in the blood dropped to a 30% from its optimal antiparkinsonian effect. This dystonia can respond to either increase in the daily levodopa dose or the number of doses. In one case series, 41% of patients with off period dystonia resolved immediately after implantation of bilateral subthalamic nucleus (STN), presumably from its lesioning effect (11). BoNT has also been used to treat this phenomenon effectively (5). Continuous levodopa duodenal infusion has also been reported to be beneficial in treating the dystonia (12).
2.5 Other types of dystonia

2.5.1 Blepharospasm
This is characterized by involuntary forceful eyelid closure. It is rarely present in idiopathic PD, especially in its pure form. More often than not, when is present, it is associated with apraxia of eyelid opening—characterized by difficulty in voluntarily opening the eyes, sometimes with the patients needing to use their thumb and index finger to open their eyes. In both instances, BoNT is the treatment of choice.

2.5.2 Bruxism
This can be classified as a form of oromandibular dyskinesia, and can lead to headache, teeth destruction and temporomandibular joint disease. Long term use of levodopa is known to cause this. This phenomenon has also been successfully treated with BoNT.

2.5.3 Camptocormia
This characterized by involuntary and often forceful forward bending of the trunk. Patients often feel like something is pulling them to bend forward. This responds poorly to levodopa or dopamine agonist (DA). However there is a report of camptocormia responsive to levodopa treatment (13). Unfortunately, anti-spasticity medications have shown no benefit on this challenging condition (5). If there is EMG evidence of abdominal rectus contraction, BoNT has proven to be an effective treatment (5).

2.5.4 Pisa syndrome
This refers to the forceful lateral flexion of the trunk. It can involve the head and neck as well. It can be idiopathic, related to antipsychotic treatment, and more recently described in neurodegenerative disorders, especially in the setting of cholinesterase inhibitor, selective serotonin reuptake inhibitor or antiparkinsonian treatment (14). Improvement of this condition has been reported with treatment with BoNT alone or in conjunction with physical therapy/rehabilitation treatment (14,15). Walking aids that accentuate trunk extension and minimize flexion may provide as a sensory aid (that can transiently improve the condition while using the walker) as well as assist in gait and mobility in this condition. In one study, Pisa syndrome was most often observed in relation to changes in Parkinsonian regimens (16). This can occur when increasing or decreasing dopaminergic stimulation by either increasing or decreasing dosages or adding or eliminating medications. In this particular series, prompt recognition that led to the undoing of the changes made (whenever possible) resulted in the improvement or even resolution of Pisa syndrome. The authors emphasized the importance of recognizing the onset of this syndrome before it becomes a chronic and possibly irreversible problem.

2.5.5 Anterocollis
This refers to the forward flexion of the neck and is a sign most commonly seen in MSA. However, Kashihara et al, published that anterocollis can happen in 15 out of 252 (6%) patients with PD (17).
3. Multiple system atrophy

More recently, MSA has been officially sub-classified as MSA-P if the predominant symptoms are parkinsonian, or MSA-C if the most predominant symptoms are cerebellar. Autonomic disturbance can occur in 73% of patients with this syndrome (2, 18). The dystonic features of this syndrome can affect the axial muscles and neck. They can also have dystonic movement of the toes. In one case series, they found that the frequency of dystonia in MSA was between 30.4%- 42% (1,19). Dystonia can manifest 2 to 4 years after clinical onset (2). Severe anterocollis has been associated with this syndrome and being the most common form of dystonia. It has been observed in about 25-50% of cases. However, there are some doubts as to whether this severe anterocollis is dystonic in nature. Some argue that the nature of the anterocollis could be severe and disproportionate rigidity affecting the anterior neck (1). Another possibility is that the nature of the anterocollis in MSA can be due to myopathy affecting the neck extensors (19,20). The lack of meaningful response to BoNT when injecting both sternocleidomastoid muscles (SCM) which tend to support these alternate hypotheses. The presence of dystonia in MSA has been associated with lesions in the contralateral head of the caudate. In one study, dystonia was present in 46% of MSA patients. All of the patients had focal dystonia (19). In all patients dystonia developed in the same side where the initial symptoms presented. All of these patients were exposed to levodopa, however, their response depended in part on their MSA subtype. Approximately 38% of them did not have benefit with escalating dose of levodopa up to 1200 mg/day and therapy was withdrawn. Most of these patients had MSA-C. Moreover, none of these patients developed dyskinesias. On the other hand, motor fluctuations developed in all the patients with MSA-P that responded to levodopa and 80% developed dyskinesia approximately 2 years after levodopa exposure. Dystonia developed in all but one patient with dyskinesia (19).

4. Progressive supranuclear palsy

This condition, described more than 25 years ago, often involving the geriatric population, is characterized by parkinsonism associated with early gait instability and significant, early onset ophthalmplegia affecting mostly the vertical axis. This can be manifested by the inability of the patient to perform saccades or in pursuing a target. However, this ophthalmplegia can be overcome with oculocephalics thus making it “supranuclear”. While often early in onset, this feature may not appear for up to 9 years into the disease (2). Another feature is retrocollis (involuntary extension of the neck). This also has been debated whether it is a form of dystonia or severe rigidity. The typical characteristics of dystonia are absent in the axial dystonia seen in PSP, such as: worsening during walking, when there is stress to the musculature; having a diurnal fluctuation; and, responding to sensory tricks. In one study “axial dystonia in extension” was found 17% of patients (2). None of these patients, however, presented the typical dystonic features mentioned above. For these reasons the term dystonia should be avoided in these cases. Instead, “nuchal rigidity in extension” should be adopted (21).

Blepharospasm has also been associated with PSP. It can occur as reflex blepharospasm or spontaneous blepharospasm. The frequency has been reported to be from 8% to 23%. Some scholars argue that apraxia of eye lid opening has been confused with blepharospasm. Around 50% of patients may have an associated apraxia of eyelid
opening. In one study the frequency of blepharospasm was 24% (21). There is a discrepancy when reviewing limb dystonia in pathologically confirmed cases versus clinical observation. In the former, limb dystonia seems to be a rare occurrence. In contrast, numerous clinical reports support its common occurrence (1). One study showed that the rate of dystonia in PSP was 46%, while another reported that dystonia, of any type, occurred in 62.5% of patients with PSP, with equal distribution of retrocollis and limb dystonia (1). Just one patient in this series had blepharospasm. Another study showed that limb dystonia occurred at a rate of 27% (21). Among those patients 11% had hemidystonic distribution. One unusual pattern noted was the “pointing gun” posture—when the index finger and thumb were extended (21). Only in 10% of patients did the dystonia involve a single limb (21). However, it should also be noted that in this series, most all of these patients with limb dystonia that had autopsies actually had concurrent brain diseases, the most common being cerebrovascular disease. Only 3 were shown to pathologically fulfill PSP criteria. Given these findings the authors suggested that some cases of PSP can be misdiagnosed as CBGD and vascular parkinsonism.

5. Corticobasalganglionic degeneration

The clinical features of corticobasalganglionic degeneration (CBGD) include akinesia, postural instability, limb dystonia, rigidity, tremors (postural and kinetic), cortical myoclonus, in addition of cortical sensory loss, ideomotor limb apraxia, alien hand syndrome, typically presenting (and often remaining) asymmetrically. One of the dystonic manifestations of CBGD is severe hand dystonia with some fingers extended and some flexed. However this may not be as frequent (1). Action-induced or reflex myoclonus usually accompanies dystonic posturing. In one series, all the patients with CBGD developed limb dystonia (2). Asymmetric cortical atrophy is typically seen contralateral to the most affected, dystonic side (22).

6. Miscellaneous

6.1 Dopamine transporter dysfunction

In one study Blackstone reported a mutation in the dopamine transporter (DAT) as the cause of infantile parkinsonism-dystonia syndrome (23). This syndrome is usually present in infancy with slowness of movement, rigidity and rest tremor. Dystonia accompanies the parkinsonism. This protein is involved in the reuptake of dopamine from the synaptic cleft to the presynaptic neuron. This mutation is associated to a loss of function thereby impairing dopamine reuptake. In this study, the affected patients showed increased levels of dopamine metabolites such as homovanillic acid in the cerebrospinal fluid (CSF). This drove the conclusion that the excess of dopamine in the synaptic left can 1) deplete intracellular stores of dopamine, 2) down regulate the postsynaptic receptors and 3) activate D2 presynaptic receptors to further decrease the synthesis of dopamine (23).

However there have been other cases of infantile parkinsonism-dystonia where no mutations in the DAT have been identified. There is a wide range of presentation of the disease. Ocular flutter (involuntary burst of eye movement around a point of fixation), and saccade initiation failure have also been reported (23,24).
6.2 Dopamine responsive dystonia

The cause of dopamine responsive dystonia (DRD) is a hereditary deficiency in the dopamine pathway. These patients tend to have a brisk response to low dose levodopa. Two mutations will be mentioned—one affecting the enzyme GTP cyclo-hydrolase (GTPCH) or DYT5a. This mutation is inherited in an autosomal dominant pattern. The other is tyrosine hydroxylase (TH) or DYT5b, which seems to be inherited recessively. These also are more severe and more complex than the typical DRD.

One characteristic feature is the diurnal fluctuations, with symptoms getting worse as the day progresses, and improving after sleep. It most commonly presents in the first decade of life, typically involving the legs first, then gradually generalizing. However, when presenting later, parkinsonian symptoms may be observed. The presentation of children with TH mutations are more complex. These patients can have mental retardation, oculogyric crisis and hypotonia (25).

6.3 Wilson's disease

This is a recessively inherited condition due to mutations in the ATP7B gene. It can present mostly in the first decade of life but later presentations, usually before the age of 50, have been reported. It is often associated with liver disease and psychiatric disorders. Movement disorder presentations include: dystonia, ataxia, tremors, chorea, and parkinsonism. Cooper studies are necessary for the diagnosis. Serum copper is unreliable in Wilson’s disease. The more reliable work up includes: 24 hour urine copper, serum ceruloplasmin, and a slit lamp examination looking for Kayser-Fleischer rings. MRI of the brain can show variety of abnormalities that affect the basal ganglia, brainstem, white matter and thalamus. Genetic testing is available but can be complicated by individual mutations specific to a family (25).

6.4 PARK2-Parkin

Mutations in this gene cause autosomal recessive young-onset parkinsonism. The symptomatology of PARK2 patients is very similar to idiopathic PD. However there is the thought that PARK2 patients have intact sense of smell (25). Dystonia can be present and can be the presenting symptom in about 40% of patients. It typically affects the lower extremities.

6.5 PARK6- PTEN-induced putative kinase 1 (PINK1)

Mutations in this gene can also cause autosomal recessive inherited parkinsonism. It is of slow progression and typically with a sustained response to levodopa. Foot dystonia, urinary urgency, orthostatic hypotension, cognitive disorders and psychiatric disorders have also been described (25).

6.6 X-linked dystonia and parkinsonism (Lubag)

As the name implies this is an X-linked inherited syndrome characterized by the onset of dystonia affecting the craniocervical region, trunk, or the distal limbs and later progressing to develop parkinsonism (26). The dystonic manifestations are diverse, including oromandibular, lingual, cervical, truncal, foot and limb dystonia. (27,28). It is minimally responsive to
medication. It is very prominent in Philippines, particular among inhabitants and descendants from the Island of Panay (29). Within 5 years it can progress to generalized dystonia. Parkinsonism may not be the only accompanied symptoms but myoclonus, chorea, focal tremor, and myorhythmia may be present. Females may also be affected but in a much milder form (25). MRI may show signal abnormalities in and mild atrophy of the caudate and putamen during the beginning of the disease. However when parkinsonian symptoms develops there is much more striking atrophy and signal abnormalities in those structures.

Treatment can be challenging since antipsychotics, anticholinergic and antiparkinsonian drugs are not consistently effective (30). However BoNT may give temporary relief of the dystonia (25,27,28). There is one report of Zolpidem to be effective in treating the dyskinesia, dystonia and akinesia in a patient with XDP. There are some reports that DBS implantation in bilateral globus pallidus internus improved the dystonia in this syndrome (26,30). However one of this reports showed no benefit in the patient’s parkinsonism (26).

6.7 Other disorders that can present with dystonia-parkinsonism

1. PARK7- DJ1
2. Neurodegeneration with Brain Iron Accumulation (NBA)1-Pantothenate Kinase-associated Neurodegeneration (PKAN)
3. NBIA 2 Associated with PLA2G6 gene mutation/PARK 14
4. PARK 9- Kufor-Rakeb Disease
5. SENDA syndrome
6. Neuroferritinopathy
7. PARK15-FBXO7-associated neurodegeneration
8. DYT16
9. Rapid onset dystonia Parkinsonism (DYT12)
10. Spatacsin (SPG11)

7. Conclusions

Dystonia in parkinsonian disorders is a well-recognized entity. For the most part the diagnosis of a parkinsonian syndrome is largely clinical. This makes the classification of patients challenging at times. Symptoms can overlap between different parkinsonian disorders. Complicating this picture is that dystonia can occur in primary parkinsonian conditions, and parkinsonism can occur in primay dystonic conditions. Recent advancements on genetics have challenged our traditional classification of parkinsonian and dystonic conditions based on clinical presentation. Organized data of pathologically-confirmed cases are wanting. More extensive studies with larger patient cohorts with pathological and/or genetic confirmation are needed. Finally, treatment of dystonia in parkinsonian conditions remain challenging, despite the growing utilization of BoNT and the promise of DBS surgery.

8. References


Dystonia has many facets, and among those, this book commences with the increasingly associated genes identified, including a construct on how biology interacts with the dystonia genesis. The clinical phenomenology of dystonia as approached in the book is interesting because, not only were the cervical, oromandibular/lingual/laryngeal, task-specific and secondary dystonias dealt with individually, but that the associated features such as parkinsonism, tremors and spasticity were also separately presented. Advances in dystonia management followed, and they ranged from dopaminergic therapy, chemodenervation, surgical approaches and rehabilitation, effectively complementing the approach in dystonia at the clinics. A timely critical pathophysiologic review, including the muscle spindle involvement in dystonia, is highlighted at the book's end.

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