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Review

Dystonia and Parkinson's disease: What is the relationship?

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ABSTRACT

Dystonia and Parkinson's disease are closely linked disorders sharing many pathophysiological overlaps. Dystonia can be seen in 30% or more of the patients suffering with PD and sometimes can precede the overt parkinsonism. The response of early dystonia to the introduction of dopamine replacement therapy (levodopa, dopamine agonists) is variable; dystonia commonly occurs in PD patients following levodopa initiation. Similarly, parkinsonism is commonly seen in patients with mutations in various DYT genes including those involved in the dopamine synthesis pathway. Pharmacological blockade of dopamine receptors can cause both tardive dystonia and parkinsonism and these movement disorders syndromes can occur in many other neurodegenerative, genetic, toxic and metabolic diseases. Pallidotomy in the past and currently deep brain stimulation largely involving the GPi are effective treatment options for both dystonia and parkinsonism. However, the physiological mechanisms underlying the response of these two different movement disorder syndromes are poorly understood. Interestingly, DBS for PD can cause dystonia such as blepharospasm and bilateral pallidal DBS for dystonia can result in features of parkinsonism. Advances in our understanding of these responses may provide better explanations for the relationship between dystonia and Parkinson's disease.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by a movement disorder (i.e., the clinical syndrome of parkinsonism) as well as a wide variety of non-motor features, typically related to the deposition of alpha synuclein. The cause is largely unknown; the interaction of various genetic and environmental factors is usually proposed. However, PD is highly heterogeneous (e.g., clinical, genetic, pathology), suggesting that it is not a single disorder. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (Jinnah and Albanese, 2014). Dystonia is well recognized to be due to a large number of different causes; it can occur as an isolated clinical feature or can be associated with other neurological deficits, particularly in disorders that manifest parkinsonism (Albanese et al., 2013).

Dystonia and Parkinson's disease are closely linked. Flexion postures of limbs and trunk are a primary manifestation of PD and were especially prominent in the pre-levodopa era. These sometimes resulted in marked deformities mistaken for joint diseases such as rheumatoid arthritis (MacFarlane and Dieppe, 1983). As discussed below, older literature often considered this as a form of dystonia (Denny-Brown, 1962; Denny-Brown, 1968), however, these postures are generally distinct from the movement disorder(s) now subsumed under the term dystonia (Albanese et al., 2013). Dystonia can be seen in 30% or more of patients with Parkinson's disease and it is more prevalent when the onset of parkinsonism is before the age of 40 (Kidron and Melamed, 1987; Hartmann et al., 1998; Quinn, 1993; Carella et al., 1993; Ishikawa and Miyatake, 2018). The dystonia can precede clinical symptoms of Parkinson's disease by almost a decade (Poewe et al., 2018; LeWitt et al., 1986). As indicated, parkinsonism and dystonia co-occur in a variety of disorders and, indeed, parkinsonism is commonly seen with mutations in DYT genes (e.g., DYT/PARK-*TAF1* (DYT3), DYT/PARK-*ATP1A3* (DYT12), DYT/PARK-*PRKRA* (DYT16) including those involved in the dopamine synthesis pathway (e.g., DYT/PARK-*GCH1* (DYT5a), DYT/PARK-*TH* (DYT5b) (Phukan et al., 2011; Wijemanne and Jankovic, 2015; Marras et al., 2016).

2. Pathophysiological overlap

The pathophysiology of dystonia is not entirely understood and various theories and models have been proposed. Older hypotheses emphasized firing rates of neurons (Bergman et al., 1998) in the direct and indirect pathways involving the cortex-basal ganglia and thalamus

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have suggested opposite states in dystonia and parkinsonism. Recent reviews have highlighted the importance of spatial and temporal patterns of activity in the GPi and STN in generating normal movements rather than the levels of output from these nuclei. Microelectrode recorded local field potentials (LFP) recordings from the GPi in patients with dystonia have demonstrated relatively high power in the 3- to 12-Hz frequency range compared to other frequency bands. These low-frequency oscillations have been suggested to be responsible for the pathophysiology of dystonia (Chu Chen et al., 2006).

In PD, the LFP recorded during STN DBS surgery have demonstrated an increased oscillatory activity in the beta frequency band. The beta band is thought to be antikinetic and is abolished with dopaminergic therapy (Brown et al., 2001; Alegre et al., 2005; Silberstein et al., 2003), and DBS(Ray et al., 2008). The degree of clinical improvement correlates with the beta band suppression (Weinberger et al., 2006; Kühn et al., 2009). Along with suppression of beta band, there is an increase in theta, gamma and high-frequency band following dopaminergic therapy in PD (Brown et al., 2001; Foffani et al., 2003; Kane et al., 2009). Thus, there is an elevated relative power of the beta spectrum in PD, while the beta power is diminished in dystonia. The relative power in the 4- to 10-Hz frequency band is higher in dystonia compared to that reported in both treated and untreated PD (Silberstein et al., 2003). In addition to the above findings, less coherence between single-unit activity and LFP oscillations was noted in dystonia in comparison to PD patients and synchronization between neurons firing at beta frequencies is more prominent in PD than dystonia(Weinberger et al., 2012).

In addition to the “firing rate model” and “firing pattern model” (Bergman et al., 1998), reduced movement-related inhibition (“dynamic activity model”) (Nambu et al., 2015) in the GPi has also been proposed. In the case of dystonia, signals through the hyperdirect, direct, and indirect pathways may cause a sequence of bursts and pauses in the GPi, with subsequent inhibition and rebound bursts in the thalamus and cortex leading to involuntary movements (“dynamic activity model”).

The mechanism of underlying pathophysiological benefits for DBS is poorly understood, and various hypotheses (inhibition hypothesis, excitation hypothesis, and disruption hypothesis) have been proposed to explain the physiological mechanism of DBS (Vitek, 2008; Chiken and Nambu, 2015). It is unclear from our understanding of these pathophysiological changes in the basal ganglia how or why dystonia and parkinsonism can co-occur and why they can both respond to lesion/DBS surgery. Confirming this state of ignorance, one review simply stated “GPi-DBS blocks abnormal information flow responsible for motor symptoms in both diseases” (Chiken and Nambu, 2015). To add the conundrum, chronic GPi DBS stimulation can sometimes paradoxically lead to parkinsonism in patients treated for dystonia (Zauber et al., 2009). This may be related to the distinctive outcomes of stimulation of different functional zones within the Gpi; ventral GPi stimulation is associated with improvement in dystonic symptoms at the possible cost of DBS-induced parkinsonism (Krack et al., 1998). Future explanations need to incorporate more recent concepts of dystonia as a network disorder involving the basal ganglia-cerebello-thalamo-cortical circuit (Poston and Eidelberg, 2012), as supported by many neuroimaging studies (e.g., FDG- PET, DTI), (Argyelan et al., 2009; Neumann et al., 2017) and the perhaps more recent proposals of the role of the cerebellum in the pathogenesis of dystonia (Kaji et al., 2018; Bologna and Berardelli, 2018, 2017).

Recent studies, including the evaluation of local field potentials, have also suggested dysfunction of the spatial and temporal patterns of activity involving the SNr and the GPi, which modulate normal movements in both PD and dystonia (Vitek, 2008). In PD as well as dystonia, there is an alteration in both long-term potentiation and long-term depression modulating synaptic plasticity. Studies in PD mouse models have shown an absence of LTD in the striatum of dopamine-denervated mice and blocking of corticostriatal LTP in chronically dopamine denervated mice (Centonze et al., 1999). The studies in animal models of dystonia have shown reduced LTD and increased LTP corticostriatal projections. These changes in the LTP and LTD can lead to abnormal motor activity (Calabresi et al., 2016).

The dopaminergic system provides an important link between PD and dystonia. Reduced activity of the nigrostriatal dopamine system can cause both dystonia and parkinsonism. For example, pharmacological blockade of dopamine receptors can cause acute and tardive dystonia and drug-induced parkinsonism. Parkinsonism in monkeys induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is associated with foot dystonia similar to early PD (Perlmutter et al., 1997). Similarly, mouse models have shown the presence of dyskinesia and dystonia after 6-OHDA injections into the sensorimotor striatum (Lundblad et al., 2004). Many disorders combining dystonia and parkinsonism, including PD, are characterized by reduced levels of striatal dopamine due to loss of SNc neurons. Similarly, genetic disorders resulting in deficiencies of the enzymes involved in the dopaminergic synthesis pathway can present with dopa-responsive dystonia (DRD), parkinsonism in isolation, or both. Reduction in nigrostriatal dopamine results in increased activity of striatal cholinergic interneurons that regulate the activity of the striatal spiny projecting neurons which can give rise to abnormal striatal plasticity underlying both parkinsonism and dystonia (Dang et al., 2012; Healy et al., 2008a). There are also suggestions that two different affinity states of dopamine receptors could account for different clinical phenotypes. In the event of a marginal deficiency of dopamine or levodopa, the high-affinity receptors are stimulated without stimulation of the low-affinity receptors leading to dystonia in the absence of parkinsonism. When the dopamine depletion is severe, even the high-affinity receptors are not stimulated which leads to both parkinsonism and dystonia (Jankovic and Tintner, 2001).

Large spiny cholinergic interneurons in the striatum also play a key role in direct and indirect pathways, modulating their output by influencing striatal dopaminergic and glutamatergic projections or by directly modulating striatal output via cholinergic receptors located on the medium spiny neurons (Calabresi et al., 2014). The concept of reciprocal interactions between dopamine and acetylcholine in the striatum was suggested in the 1960's and 1970's. Recent work supports the role of striatal cholinergic transmission in the control of voluntary movements (Bonsi et al., 2011) and dysfunction of acetylcholine release in the striatum is believed to be an important contributor to the symptoms of Parkinson's disease and dystonia (Pisani et al., 2007).

Another aspect of striatal anatomy and the nigrostriatal dopamine system that could contribute to dystonia in PD relates to the striatal striasomal-matrix microstructure. Striosomes occupy 10–15% of the striatum with a caudo-rostral gradient, richest in the rostral striatum, while the dorsolateral (motor) putamen is mainly comprised of matrix (Johnston et al., 1990; Desban et al., 1993). Theoretically, patients with dystonia in PD (early or late) could have an imbalance in the activity of striosomal vs matrix spiny neurons, possibly due to more selective disturbances of nigrostriatal dopamine input to these regions (Sato et al., 2008). This concept has been discussed with respect to other forms of dystonia including that seen in advanced PD and in levodopa-induced dyskinesia, as well as in other diseases such as Huntington's disease and X-linked dystonia parkinsonism DYT/PARK- *TAF1* (DYT3) (Goto et al., 2005; Crittenden et al., 2016).

Other neurotransmitters such as serotonin, acetylcholine, and glutamate may also play a role in patients presenting with parkinsonism and dystonia (Chase and Oh, 2000).

3. Dystonia in PD

Parkinson's disease is associated with a variety of types of dystonia. We will begin this discussion with some general concepts and categories and then go on to a discussion dividing the dystonia into anatomical subtypes. This will be followed by a more detailed discussion of

dystonia occurring in specific genetic forms of PD.

The dystonia in PD infrequently occurs as a presenting symptom or an associated symptom in untreated PD patients. As mentioned earlier, dystonia as an initial manifestation, is more common in young-onset PD (LeWitt et al., 1986) and especially in autosomal recessive genetic parkinsonisms such as with PARK-*PARKIN* (PARK2) and PARK-*SNCA* (PARK1) mutations. Early dystonia can have a variety of focal and segmental distributions, particularly involving the lower limb. Exertion (e.g., walking) may be a precipitant or trigger for the dystonia. Patients can also develop fixed painless contractures of limbs, which are also thought to be dystonic. Dystonia can precede the development of parkinsonism from anywhere between 1 and 25 years but on an average 10 years in one review (Tolosa and Compta, 2006), although this is considerably longer than in our experience. The response of early dystonia to the introduction of dopamine replacement therapy (levodopa, dopamine agonists) is also variable; it can worsen, improve or remain unchanged (LeWitt et al., 1986); some have suggested a better response to dopamine agonists but this benefit is inconsistent.

More commonly, dystonia occurs in PD patients sometime after levodopa has been initiated. A variety of patterns of levodopa-associated dystonia occur in PD: when the medication is wearing off, at peak dose or at the onset and/or off-set of benefit as a part of diphasic dyskinesia. Approximately 30% of the PD patients treated with levodopa develop "off- dystonia (Kidron and Melamed, 1987). One common variant of this occurs in the morning before the first dose is taken. In contrast to the other varieties, off-dystonia is commonly painful. Off-dystonia is more common in the foot (Melamed, 1979) while peak-dose dystonia involves the neck, face and upper limbs. The dystonia occurring as part of diphasic dyskinesia tends to involve the lower limbs. Dystonia can also occur in patients who have undergone DBS as a consequence of stimulation but the majority of these symptoms are secondary to the diffusion of the current into the corticospinal or corticobulbar fibres (Baizabal-Carvallo and Jankovic, 2016). "Apraxia of eyelid opening", which in many patients is probably a form of pre-tarsal blepharospasm (as supported by response to pre-tarsal injections of botulinum toxin), is seen in 2–31% of the patients undergoing STN DBS (Tommasi et al., 2012; Fuß et al., 2004; Umemura et al., 2011). Occasionally this symptom responds to levodopa (Umemura et al., 2008) or lowering stimulation parameters or increasing the frequency of the stimulation (Strecker et al., 2008) (Table 1).

3.1. Blepharospasm in PD

Blepharospasm and "eyelid opening apraxia" are more common in atypical parkinsonian syndromes than in PD. The incidence of blepharospasm in PD has been reported between 0.9%–3.26%; it may very rarely precede the disease and can be levodopa responsive (Rana et al., 2012; Yoon et al., 2005). There is a single case report of Meige syndrome in Parkinson's disease (Mark et al., 1994).

3.2. Camptocormia, Pisa syndrome and anterocollis in PD

Camptocormia refers to extreme flexion of the trunk while sitting which worsens on walking and improves in the supine position (Jankovic, 2010). Although recognized since the time of Charcot, the first case series in PD was reported in 1999 by (Djaldetti et al., 2001). Camptocormia may improve with a geste antagoniste, botulinium toxin (von Coelln et al., 2008; Azher and Jankovic, 2005) and DBS surgery suggesting dystonia as a possible explanation in at least a proportion of cases (Sako et al., 2009). Similarly EMG studies have shown excessive activation of abdominal muscles (Bloch et al., 2006). Abnormal control of the reticulospinal tract by the basal ganglia has been proposed as a pathogenic mechanism (Lepoutre et al., 2006). Abdominal, hip and spine surgery have been described as the triggering events for the camptocormia (Djaldetti et al., 2001; Bloch et al., 2006; Lepoutre et al., 2006; Tiple et al., 2009).

Anterocollis refers to a forward flexion of the head and neck. It can be mild and be seen as a part of the stooped posture of PD; severe anterocollis is usually associated with disproportionate flexion of the head and neck in comparison to the posture of the limbs and trunk (Quinn, 1989; van de Warrenburg et al., 2007a). Anterocollis is more common in Multiple System Atrophy (MSA) with a prevalence of 42.1% (Ashour and Jankovic, 2006) while a much lower prevalence is reported in PD (5.8%) (Kashihara et al., 2006; Fujimoto, 2006). It affects certain ethnicities more frequently, with a higher prevalence of case reports from Japan. Anterocollis in PD and MSA does not improve with sensory tricks (Boesch et al., 2002). It is more commonly seen in long-standing cases of PD, where it is often combined with pronounced head tilt and possibly some rotation, but rarely can present before the onset of motor symptoms of PD (Kashihara et al., 2006).

Pisa syndrome is characterized by marked lateral flexion of the trunk, which resolves on lying down. It was previously described as an adverse effect of dopamine blocking agents (Ekbom et al., 1972) but it is now known to be associated with PD (Villarejo et al., 2003). Scoliosis is more prevalent in PD than in the general elderly population (prevalence of 8.5–60% in PD) (Ashour and Jankovic, 2006; Baik et al., 2009; Serratrice and Schiano, 1976; Grimes et al., 1987; Duvoisin and Marsden, 1975). Pisa syndrome may precede scoliosis in PD. Pisa syndrome may have a variable response to botulinum toxin (Bonanni et al., 2007) and DBS surgery (Umemura et al., 2010). Occasionally patients respond to the combination of DBS surgery and levodopa (Artusi et al., 2017). There are rare reports of development of Pisa syndrome following pallidotomy (Spanaki et al., 2010; van de Warrenburg et al., 2007b). However, these were secondary to malplaced pallidotomies (van de Warrenburg et al., 2008). Complex corrective spinal surgery can successfully improve the camptocormic posture but is associated with a very high complication rate (Chan et al., 2018; Wadia et al., 2011).

Some cases of camptocormia (Mano, 2018), Pisa syndrome (Cannas et al., 2009) and particularly anterocollis, seem to be induced by changes in dopaminergic therapy, particularly dopamine agonists (even chronic therapy that had, to date, been tolerated well), as supported by resolution of the symptoms on drug withdrawal (Prakash and Lang, 2007). Anterocollis has also been reported secondary to levodopa and amantadine (Kataoka and Ueno, 2011; Dohm et al., 2013; Taguchi et al., 2008), as an "off" phenomenon (Guduru et al., 2017) or secondary to dyskinesia due to dopaminergic therapy associated with fluctuations in anterocollis (Doherty et al., 2011). Postural deformities in PD may be secondary to central mechanisms like dystonia, rigidity and proprioceptive disintegration while peripheral causes such as myopathy and skeletal and soft tissue changes may also play a role (Doherty et al., 2011). Indeed, it is still debated whether the development of camptocormia and anterocollis are secondary to dystonia, myopathy (Spuler et al., 2010; Laroche and Cintas, 2010; Margraf et al., 2010) or both.

3.3. Limb dystonia in PD

Around 10–15% of PD cases present with focal dystonia of the limbs (Wickremaratchi et al., 2011). Involvement of the lower limb is more common than upper limb. Lower limb dystonia can be the initial presentation of typical "idiopathic" Parkinson's disease, young-onset genetic parkinsonism (PARK-*PARKIN* (PARK2), PARK-*PINK1* (PARK6), PARK-*DJ1* (PARK7) mutations) and dopa-responsive dystonia, clearly highlighting common dopaminergic pathophysiological mechanisms (Healy et al., 2008b; Schneider et al., 2006; Elia et al., 2014; Chang and Josephs, 2013). Very rarely, paroxysmal exercise-induced dystonia can be the presenting symptom or be part of the clinical syndrome of PD, particularly in young onset cases as due to PARK-*PARKIN* (PARK2) gene mutations (Erro et al., 2014). Patients can demonstrate a "pseudo-foot drop gait" secondary to the action dystonia of the plantar flexors and the foot invertors triggered while walking (Aquino et al., 2015).

Table 1
Summary of dystonia in Parkinson's disease.

Type of dystonia	Frequency of dystonia in PD	Differential diagnosis	Characteristics	Treatment
Blepharospasm	0.9–3.26% (Baizabal-Carvallo and Jankovic, 2016; Tommasi et al., 2012)	–	- May precede PD. - Commonly associated with eyelid opening apraxia.	- May respond to levodopa and fluctuate with treatment response. - Good response to Botulinium toxin.
Eyelid opening apraxia	0.7% in PD(Tommasi et al., 2012) 2–31% in STN DBS(Goto et al., 2005; Crittenden et al., 2016; Chase and Oh, 2000)	–		- May respond to levodopa. - Reducing stimulation and increasing frequency in STN DBS patients. - Good response to Botulinium toxin (pretarsal injections).
Camptocormia	3–17.6%(Djaldetti et al., 2001; Sako et al., 2009)	1) Concomitant myopathy Anterior horn cell disease. (associated with trunk extension weakness) 2) Fixed deformity - Ankylosing spondylitis - Vertebral pathology - Syrinx - Idiopathic or degenerative scoliosis.	- More common in advanced PD. - Triggers - Abdominal, spine, hip surgery. - changes in dopaminergic therapy - chronic dopaminergic therapy (specially dopamine agonist).	- Rarely responds to levodopa. - Botulinium toxin – variable response. - DBS- varied outcomes.- - Spinal surgery (last resort)
Anterocollis	5.3–6.0%(Bloch et al., 2006; Lepoutre et al., 2006)	1) Concomitant myopathy Anterior horn cell disease. 2) Cervical spine pathology.	More common in advanced PD. Triggers - changes in dopaminergic therapy - chronic dopaminergic therapy (specially dopamine agonist). - Off-period dystonia. - As a manifestation of levodopa-induced dyskinesia	- Botulinium toxin may be helpful. - Withdrawal of dopamine agonist. - Clonazepam (one case report) - DBS - Spine fusion (last resort)
PISA syndrome/scoliosis	8.5–60%(Sako et al., 2009; Ashour and Jankovic, 2006; Kashihara et al., 2006; Fujimoto, 2006; Boesch et al., 2002) (scoliosis)	Atypical parkinsonism - MSA	Triggers - 4-9 years after pallidotomy (2 case reports) - Drugs - changes in dopaminergic therapy - chronic dopaminergic therapy (specially dopamine agonist). - Initiation of dopaminergic medication. Other drugs: valproic acid, antidepressants and cholinesterase inhibitors	- Botulinium toxin. - Optimization of dopaminergic therapy. - STN DBS - inconclusive. - Clozapine.
Limb dystonia	10–15%(Taguchi et al., 2008)		1) Task specific/action-induced dystonia Upper limbs – writer's cramp, musician's dystonia. Lower limbs: pseudo foot drop gait. 2) Paroxysmal exercise-induced dystonia. Related to medications: Off dystonia. Diphasic dyskinesia.	- Botulinium toxin. - Optimization of dopaminergic therapy.

Dystonia of the upper limb in PD can be task specific although non-task specific dystonia is more common. Both musician's dystonia and task-specific writing tremor preceding the development of overt Parkinson's disease have been described (Smith et al., 2014; Castro Caldas et al., 2016).

Deformities of the limb (often referred to as "striatal" postures) were originally described by (Charcot, 1877) and (Purves-Stewart, 1898) in patients with Parkinson's disease. Their true prevalence is unknown. It is unclear whether some of these abnormal postures represent forms of dystonia; older literature sometimes described "flexion dystonia" of PD, or "hemiplegic dystonia" of pyramidal tract lesions, which are now clearly distinguishable from the modern concept of dystonia. Given some uncertainty in the origin and classification of "striatal limbs" we will discuss these features briefly here. As will be seen, there is clear overlap between these postures and dystonia, especially in the case of the "striatal toe".

The typical deformity seen in the "striatal hand" is the flexion of the metacarpophalangeal joints, extension of the proximal interphalangeal joints, flexion of the distal interphalangeal joints, and ulnar deviation (Gortvai, 1963). Striatal hand deformities in PD have been reported in 12.8% in one series (Ashour and Jankovic, 2006) while 24% in another series (Reynolds and Petropoulous, 1965). While Kyriakides and Langton reported only 3 cases of hand deformity in PD over a one year period at a "busy" neurology department (Kyriakides and Hewer, 1988). The variability in these numbers may be related to a variable definition of striatal hand in these series.

In contrast to dystonia associated with PD, which classically worsens with activity and disappears during sleep, the striatal hand is present at rest and persists during sleep. Untreated dystonia can develop fixed postures, which are different from striatal posturing. Rigidity (Kyriakides and Hewer, 1988) and dystonia (Tolosa & Compta, 2006) have been postulated as the mechanism for these postures, but the exact mechanism is still debated. Striatal hand is classically seen in advanced PD but can also be seen in early stages typically associated with mild flexion of metacarpophalangeal joints of the hand (Ashour and Jankovic, 2006; Ashour et al., 2005). The striatal hand can cause disfigurement, pain, and loss of function in severe cases. Flexion deformities of the fingers can cause skin erosions and secondary infections in the palm.

The "striatal foot" is associated with hallucal hyperextension, flexion of the other toes and ankle inversion (Ashour and Jankovic, 2006). The flexion of the toes typically described as the toe-curling symptom is usually associated with pain and cramps. It also impairs the ability to wear shoes, walk and stand. It occasionally can cause ulceration and bone erosion. It can precede levodopa therapy in 2.4%- 8% of the patients (Kidron and Melamed, 1987; Nausieda et al., 1980) and needs to be differentiated from dystonia associated with levodopa therapy. An isolated "striatal toe" is a subtype of striatal foot in the absence of the equinovarus foot. It needs to be differentiated from the Babinski sign which is usually associated with toe fanning and flexion synergy of other muscles in the same leg along with hallucal hyperextension (Winkler et al., 2002). Dystonia, rigidity (Kyriakides and Hewer, 1988) and inappropriate muscle contraction (Hu et al., 1999) may be responsible for the striatal foot.

Striatal limbs rarely respond to antiparkinsonian drugs, but there are some case reports of complete resolution of striatal hand with levodopa treatment (Ashour et al., 2005) and the apparent current low incidence of the striatal hand and Parkinsonian hand deformities in particular, suggests that modern dopaminergic therapy may prevent the occurrence of these features, which were more common in the pre-levodopa era. On the other hand, rarely, dopaminergic drugs previously used in PD (pergolide and bromocriptine) were associated with reactive fibrosis sometimes leading to limb contractures (Quinn et al., 1988). Other medications like anticholinergics, baclofen, and benzodiazepines have been successful in treating foot dystonia but their response in striatal limbs has not been reported. Botulinum-toxin injection has been used successfully in the treatment of striatal toes (Giladi et al., 1994; Jankovic, 2004). Botulinum-toxin injection for striatal hand, especially into the lumbricals and short adductors of the thumb, has led to functional improvement, pain relief and prevention of injuries secondary to finger contractures (Cordivari et al., 2001). Improvement in striatal limb deformities has been reported with neurosurgical treatments such as thalamotomy (Gortvai, 1963), and DBS (Morishita et al., 2008). Orthopedic surgical interventions and spints can be attempted if conventional non-operative treatments are unsuccessful (Moore et al., 1998).

3.4. Cervical dystonia in PD

Typical cervical dystonia (distinct from anterocollis) rarely can be the presenting symptom and can precede other features of PD by 5.8 ± 7.6 years with mean age of onset of parkinsonism of 49.1 ± 10.1 years (Papapetropoulos and Singer, 2006). Torticollis (rotation) has been the most common phenotype seen in the patients with PD. These patients have responded well to the botulinium toxin and generally have not experienced worsening of dystonia with initiation of the levodopa treatment (Papapetropoulos and Singer, 2006).

4. Genetic PD syndromes and dystonia

4.1. Autosomal dominant

4.1.1. Park-SNCA (PARK1)

PARK-*SNCA* (PARK1) related PD can be secondary to mutations or multiplications of the alpha synuclein gene. This form of genetic PD is characterized by earlier age of onset of disease and motor fluctuations with a higher prevalence of non-motor symptoms and relatively early decline of levodopa responsiveness (Oczkowska et al., 2013). In a recent meta-analysis, dystonia was noted in 12 out of 146 cases along with features of parkinsonism (Trinh et al., 2018). Dystonia may be seen earlier in the disease course in comparison to sporadic PD. Foot and cervical dystonia along with blepharospasm have been reported in these patients (Kiely et al., 2015; Konno et al., 2016).

4.1.2. Park-LRKK2 (PARK8)

PARK-*LRKK2* (PARK8) mutations are the most common genetic cause of PD. In a case-control study of patients with PARK-*LRKK2* (PARK8) conducted in 21 centers the incidence of dystonia was 42% (126 out of 301), the majority of them with "off period" foot dystonia early in the disease (Healy et al., 2008a). Rarely, patients with blepharospam, arm, neck and lingual dystonia have been reported with PARK-*LRKK2* (PARK8) mutations (Healy et al., 2008a). A recent meta-analysis showed a similar incidence of dystonia (38%; 61 out of 161 cases) (Trinh et al., 2018).

4.1.3. Park-GBA

Gaucher's disease is an autosomal recessive disorder secondary to mutations in the PARK-*GBA* gene. Both homozygous and heterozygous mutations confer significant risk for the development of PD. Parkinsonism secondary to PARK-*GBA* mutations is associated with earlier age of onset, higher incidence of cognitive impairment and rapid motor decline (Brockmann et al., 2011; Brockmann et al., 2014; Beavan et al., 2015).

Dystonia has not been specifically reported in patients with parkinsonism secondary to PARK-*GBA* mutations. However, apart from the differences noted above, PARK-*GBA* -associated PD is typical levodopa-responsive Lewy body disease and so the various forms of dystonia, particularly those beginning after levodopa initiation, probably occur in a similar fashion to non-*GBA*-associated PD. Interestingly, a recent study showed an increased incidence of PARK-*GBA* mutations and decreased GBA activity in a series of patients with dystonia without parkinsonism suggesting an independent role in dystonia (Schreglmann

et al., 2018).

4.1.4. Park-VPS35 (PARK17)

PARK-*VPS35 (*PARK17) was initially reported in a Swiss family in 2008 by (Wider et al., 2008). Only two cases were reported to manifest dystonia in a recent meta-analysis of PARK-*VPS35 (*PARK17) (in most of the other 65 cases the information was not available) (Trinh et al., 2018).

4.1.5. Park-DNAJC13 (PARK19)

PARK-*DNAJC13* (PARK19) mutations were initially recognized in 2014 in a Mennonite family of Dutch–German–Russian ancestry (Vilariño-Güell et al., 2014). These mutations typically present with late-onset parkinsonism indistinguishable from sporadic PD. Dystonia seems to be very rare with these mutations. PARK-*DNAJC13* (PARK19) mutations can rarely present with lower limb dystonia (Vilariño-Güell et al., 2014).

4.2. Autosomal recessive

4.2.1. Park-PARKIN (PARK2)

Mutations in PARK-*Parkin* (PARK2*)* are probably the most commonly defined cause of early-onset Parkinson's disease (EOPD). This disorder is characterized by early dystonia (i.e., before levodopa initiation), slow progression, brisk reflexes, neuropsychiatric symptoms, the absence of Lewy bodies and an excellent response to levodopa with the early development of motor complications. In one large series dystonia was observed in 41% of the patients as an initial symptom, commonly involving the lower limbs but uncommonly also involving the neck, trunk, and hands. Eventually, 78% of patients developed dystonia at some point prior to the initiation of treatment d (Khan et al., 2003). Rarely PARK-*Parkin* (PARK2*)* mutations can present with isolated lower limb dystonia mimicking DYT-*TOR1A* (DYT1) or DRD. The foot dystonia is usually task-specific, brought out and worsened by walking or exercise and sometimes this can progress to involvement at rest (Elia et al., 2014). Occasional patients can present with foot drop dystonia (de Schipper et al., 2015).

4.2.2. Park-PINK1 (PARK6)

Mutations in PARK-*PINK1* (PARK6) are the second most common cause of autosomal recessive (AR) EOPD, and over 62 disease-causing variations have been described with this gene (Kasten et al., 2018). They have a very similar presentation to PARK-*Parkin* (PARK2*)* mutations most likely including dystonia, as described above, given the important overlapping pathophysiological mechanism of these two genes in the mitophagy pathway (Jin and Youle, 2012) but with a higher incidence of psychiatric manifestations especially depression and anxiety which are seen in 1/3rd of patients. There is very little literature on dystonia in PARK-*PINK1* (PARK6)-related PD and a review of the MDSGene database found dystonia reported in approximately 21% (29 out of 139 cases) of the patients, unrelated to levodopa in a majority of the cases (Kasten et al., 2018).

4.2.3. Park-DJ1 (PARK7)

PARK-*DJ1* (PARK7) mutations are associated with young-onset parkinsonism with 46% of the patients having associated dystonia. The dystonia in PARK-*DJ1* (PARK7) -related PD can present with early-onset lower limb dystonia (Bonifati et al., 2003a). There is a single case report of late-onset lower limb dystonia and the same patient also had predominant craniocervical dystonia (Taipa et al., 2016). Blepharospasm has been reported in few cases with PARK-*DJ1* (PARK7) mutations (Bonifati et al., 2003b; van Duijn et al., 2001).

4.2.4. NBIA/DYT/PARK-PLA2G6 (NBIA1,PARK14)

NBIA/DYT/PARK-*PLA2G6* (NBIA1,PARK14) mutations are associated with autosomal recessive phospholipase-associated neurodegeneration (PLAN). There are three main phenotypes:1) infantile-onset neuroaxonal dystrophy (INAD); 2) an atypical later-onset form (atypical NAD); and 3) young-onset dystonia-parkinsonism (PLAN-DP) (Karkheiran et al., 2015; Paisan-Ruiz et al., 2009; Kurian et al., 2008). Rarely they can present with motor symptoms after the age of 40 (Klein et al., 2016). NBIA/DYT/PARK-*PLA2G6* (NBIA1,-PARK14) patients universally present with parkinsonism and dystonia can be seen in the majority of the patients, including retrocollis/opisthotonus. Other features such as tremors, ataxia, pyramidal signs, autonomic disturbances, cognitive and behavioral issues are typically also present (Karkheiran et al., 2015; Paisán-Ruiz et al., 2012). A small proportion of patients with NBIA/DYT/PARK-*PLA2G6* (NBIA1,-PARK14) mutations have presented with pure young-onset parkinsonism, diagnosed as having PD (YOPD). Further encouraging this diagnosis has been the clear benefit obtained with levodopa and the later development of levodopa-induced dyskinesia (also features of some patients with a more obvious diagnosis of PLAN-DP). Pathologically there can be the presence of neuroaxonal dystrophy and widespread alpha-synuclein pathology with Lewy bodies and Lewy neurites particularly in the neocortex. Tau pathology can also be infrequently present (Klein et al., 2016; Paisán-Ruiz et al., 2012; Miki et al., 2017). Importantly, in some patients, the Lewy pathology has been so typical of PD that a diagnosis YOPD was reported initially and the correct diagnosis was made only much later when genetic testing became available (Klein et al., 2016; Tabamo et al., 2000).

A number of other AR disorders are associated with an atypical dystonia-parkinsonism syndrome {e.g., PARK-*ATP13A2* (PARK9), PARK-*FBX07* (PARK15) and NBIA/DYT-*PANK2* (NBIA1)} that would generally not be mistaken for the genetic parkinsonisms described above (Schneider et al., 2009) (Table 2).

5. Role of GTP-cyclohydrolase1 and Tyrosine hydroxylase mutations in PD

5.1. DYT/PARK-GCH1 (DYT5a) and PD

GTP-cyclohydrolase1(GCH1) is the rate limiting enzyme in the synthesis of tetrahydrobiopterin (BH4) which is a cofactor for tyrosine hydroxylase. Classically, GCH1 deficiency (the commonest cause of DRD) presents with lower limb dystonia in children with an excellent response to low doses of levodopa. Many of these patients demonstrate features of bradykinesia and postural instability prior to levodopa initiation. Some patients, especially those with a later presentation (even into adult life), can present a pure parkinsonian syndrome with little or no dystonia. As in patients with the classical DRD presentation, these patients typically do not develop motor fluctuations or levodopa-induced dyskinesias and have no evidence of pre-synaptic nigrostriatal degeneration (e.g., as seen on F-dopa or dihydrotetrabenazine PET or dopamine transporter SPECT). The small number of postmortem studies available confirm a lack of neurodegeneration (i.e., a normal number of nigral neurons) but reduced neuromelanin staining in the substantia nigra along with reduced levels in neopterin and biopterin in the brain (Rajput et al., 2018; Furukawa et al., 1999).

However, recently there has been increasing interest in the possible association between DYT/PARK-*GCH1* (DYT5a) mutations and a second, degenerative form of parkinsonism (Guella et al., 2015; Lewthwaite et al., 2015; Furukawa and Kish, 2015). A study by (Mencacci et al., 2014) described four families with DRD/DRD with parkinsonism or parkinsonism in isolation. The patients with parkinsonism had an abnormal dopaminergic scan suggestive of presynaptic dopamine neuronal degeneration. A whole genome study in patients with parkinsonism demonstrated that rare DYT/PARK-*GCH1* (DYT5a) coding variants were associated with a seven-fold increase in the risk of Parkinson's disease. There are also studies to suggest DYT/PARK-*GCH1* (DYT5a) to be a low-risk susceptibility locus for PD (Nalls et al., 2014).

There are other rare phenotypes reported with DYT/PARK-*GCH1*

Table 2
Dystonia in genetic PD.

Genetic mutation	Frequency of dystonia	Body part affected
Autosomal dominant		
PARK-*SNCA* (PARK1)	8.2% (Jankovic, 2004)	Foot Cervical Blepharospasm (Cordivari et al., 2001; Morishita et al., 2008)
PARK-*LRKK2* (PARK8)	38–42%(Jankovic, 2004; Moore et al., 1998)	"Off period"- foot dystonia (most common). Blepharospasm. Cervical Lingual (Moore et al., 1998).
PARK-*VPS35 (*PARK17)	Uncommon	
Autosomal recessive		
PARK-*Parkin* (PARK2)	41%- 70% (Wider et al., 2008)	Foot dystonia - Can be task-specific (worsened on walking/exercise) (Spuler et al., 2010). - Pseudo foot drop dystonia (Brockmann et al., 2011).
PARK-*DJ-1* (PARK7)	46% (Brockmann et al., 2014)	Foot (Schreglmann et al., n.d.) Craniocervical(Khan et al., 2003). Blepharospasm(de Schipper et al., 2015; Kasten et al., 2018)
PARK-*PINK1* (PARK6)	21%(Brockmann et al., 2014)	Foot dystonia
PARK-*DNAJC13* (PARK19)	Uncommon	Lower limb dystonia - unspecified (Oczkowska et al., 2013).
NBIA/DYT/PARK-*PLA2G6* (NBIA2, PARK14)	Unknown	Limb dystonia - unspecified (Bonifati et al., 2003a; Paisan-Ruiz et al., 2009)

(DYT5a) mutations. (Ceravolo et al., 2013) described three phenotypes in the same family: the index case with an MSA-like presentation, his son with young-onset classic DRD and his brother with late-onset parkinsonism mimicking PD. In another report, (Guella et al., 2015) described an 82-year-old lady with parkinsonism and an asymmetrical onset of tremors. She died at 90 years with autopsy demonstrating neurofibrillary tangles suggestive of PSP but also synuclein deposition in the brainstem. Finally, (Lewthwaite et al., 2015) described a patient presenting with adult-onset parkinsonism associated with an abnormal DAT-scan, dyskinesia and dementia. Other members of the family had pure DRD without parkinsonism and normal scans. Although it is unclear whether these rare examples are true or simply coincidental associations, they have encouraged hypotheses as to how DYT/PARK-*GCH1* (DYT5a) deficiency might predispose to a neurodegenerative process.

BH4 is a cofactor for nitric oxide synthase. Reduced levels of BH4 may cause an increase in NOS uncoupling and increased production of reactive oxygen species, which can result in oxidative stress and neurodegeneration (Giasson et al., 2000; Ryan et al., 2013). Reduced GCH1 activity can lead to mitochondrial dysfunction and alpha-synuclein aggregation. Genetic and environmental factors modulate the outcome of GCH1 deficiency. Age-related decline and chronic dopamine deficiency may eventually predispose dopaminergic cells to early neurodegeneration (Furukawa & Kish, 2015).

5.2. DYT/PARK-TH (DYT5b) and PD

Tyrosine hydroxylase is an iron containing monooxygenase enzyme catalyzing the rate-limiting step in the synthesis of catecholamines. Tyrosine hydroxylase requires tetrahydrobiopterin as a co-factor for this process.

TH deficiency can present with symptoms indistinguishable from classical dopa-responsive dystonia. It can also present with infantile parkinsonism with delayed development (Lüdecke et al., 1996; Swaans et al., 2000) or severe progressive encephalopathy (Hoffmann et al., 2003). There are a few case reports of TH deficiency presenting with levodopa-responsive myoclonus dystonia (Stamelou et al., 2012). There is a single case report of a DYT/PARK-*TH* (DYT5b) deletion leading to haploinsufficiency in a 54 year old gentleman with levodopa responsive PD in the absence of dystonia.

As with DYT/PARK-*GCH1* (DYT5a) mutations, various hypotheses have been proposed linking disturbances of TH with PD (e.g., (Kawahata et al., 2015) (Kastner et al., 1993)). To date, there have been no reported associations between PD and other genes involved in the bioamine synthesis pathway that cause varying DRD and parkinsonian phenotypes.

6. Role of DYT-*TOR1A*(DYT1) in PD

DYT-*TOR1A* (DYT1*)* mutations are responsible for early-onset, generalized dystonia (Ozelius et al., 1997). Almost all cases are due to a GAG deletion that removes 1 amino acid from torsinA (delE303) (Ozelius et al., 1997; Ozelius et al., 1989). Clinically it presents with early onset limb dystonia which later can generalize with usual sparing of the craniocervical region (Bressman et al., 2002). DYT-*TOR1A* (DYT1) never presents with parkinsonism and previous studies have failed to show the mutation in young-onset parkinsonism (Leung et al., 2001; Yang et al., 2009).

The protein Torsin A is a member of the AAA + (ATPases Associated with a variety of cellular Activities) superfamily and performs a chaperone-like function including protein trafficking, folding and membrane fusion (Breakefield et al., 2008; Standaert, 2011; Breakefield et al., 2001). TorsinA has been found in Lewy bodies which has been confirmed by immunocytochemistry, and it is postulated that Torsin A may be responsible for neuronal dysfunction in PD (Shashidharan et al., 2000; Sharma et al., 2001)Although initially promising, further studies have failed to replicate the proposed protective effects of Torsin1A in mouse models(Li et al., 2012).

7. Conclusion

Dystonia and parkinsonism coexist in a large number of neurological disorders and dopamine plays a key role in both of these movement disorder phenotypes. Dystonia is common in Parkinson's disease, manifesting a variety of temporal, somatotopic, age-related, genetic and treatment-response patterns. The underlying pathophysiological mechanisms accounting for dystonia in Parkinson's disease remain extremely poorly understood.

References

Albanese, A., Bhatia, K., Bressman, S.B., DeLong, M.R., Fahn, S., Fung, V.S.C., et al., 2013. Phenomenology and classification of dystonia: a consensus update. Mov. Disord. 28 (7), 863–873.

Alegre, M., Alonso-Frech, F., Rodríguez-Oroz, M.C., Guridi, J., Zamarbide, I., Valencia, M., et al., 2005. Movement-related changes in oscillatory activity in the human subthalamic nucleus: ipsilateral vs. contralateral movements. Eur. J. Neurosci. 22 (9),

2315–2324.
Aquino, C.C., Slow, E., Lang, A.E., 2015. Dystonic pseudo foot drop. Mov. Disord. Clin. Pract. 2 (3), 295–298.
Argyelan, M., Carbon, M., Niethammer, M., Uluğ, A.M., Voss, H.U., Bressman, S.B., et al., 2009. Cerebellothalamocortical connectivity regulates penetrance in dystonia. J. Neurosci. 29 (31), 9740 LP–9747.
Artusi, C.A., Zibetti, M., Romagnolo, A., Rizzone, M.G., Merola, A., Lopiano, L., 2017. Subthalamic deep brain stimulation and trunk posture in Parkinson's disease. Acta Neurol. Scand. 137 (5), 481–487.
Ashour, R., Jankovic, J., 2006. Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Mov. Disord. 21 (11), 1856–1863 . Aug 28.
Ashour, R., Tintner, R., Jankovic, J., 2005. Striatal deformities of the hand and foot in Parkinson's disease. Lancet Neurol. 4 (7), 423–431.
Azher, S.N., Jankovic, J., 2005 Aug 9. Camptocormia. Neurol. Int. 65 (3), 355 LP–359.
Baik, J.S., Kim, J.Y., Park, J.H., Han, S.W., Park, J.H., Lee, M.S., 2009 Jun. Scoliosis in patients with Parkinson's disease. J. Clin. Neurol. 5 (2), 91–94 . 2009/06/30.
Baizabal-Carvallo, J.F., Jankovic, J., 2016. Movement disorders induced by deep brain stimulation. Parkinsonism Relat. Disord. 25, 1–9.
Beavan, M., McNeill, A., Proukakis, C., Hughes, D.A., Mehta, A., Schapira, A.H.V., 2015. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol. 72 (2), 201–208.
Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M., et al., 1998. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci. 21 (1), 32–38.
Bloch, F., Houeto, J.L., Tezenas du Montcel, S., Bonneville, F., Etchepare, F., Welter, M.L., et al., 2006 Nov. Parkinson's disease with camptocormia. J. Neurol. Neurosurg. Psychiatry 77 (11), 1223–1228 2006/06/05.
Boesch, S.M., Wenning, G.K., Ransmayr, G., Poewe, W., 2002 Mar. Dystonia in multiple system atrophy. J. Neurol. Neurosurg. Psychiatry 72 (3), 300–303.
Bologna, M., Berardelli, A., 2017 May. Cerebellum: an explanation for dystonia? Cerebellum Ataxias 4 (1), 6.
Bologna, M., Berardelli, A., 2018. Chapter 17 - The cerebellum and dystonia. In: Manto, M., Huisman TAGMBT-H of CN (Eds.), The Cerebellum: Disorders and Treatment. Elsevier, pp. 259–272.
Bonanni, L., Thomas, A., Varanese, S., Scorrano, V., Onofrj, M., 2007. Botulinum toxin treatment of lateral axial dystonia in parkinsonism. Mov. Disord. 22 (14), 2097–2103 Aug 8.
Bonifati, V., Rizzu, P., van Baren, M.J., Schaap, O., Breedveld, G.J., Krieger, E., et al., 2003 Jn 10a. Mutations in the < em > DJ-1 < /em > gene associated with autosomal recessive early-onset parkinsonism. Science (80-) 299 (5604), 256 LP–259.
Bonifati, V., Rizzu, P., Squitieri, F., Krieger, E., Vanacore, N., van Swieten, J.C., Brice, A., van Duijn, C.M., Oostra, B., Meco, G., Heutink, P., 2003b. DJ-1(PARK7), a novel gene for autosomal recessive, early onset parkinsonism. Neurol. Sci. 24, 159–160.
Bonsi, P., Cuomo, D., Martella, G., Madeo, G., Schirinzi, T., Puglisi, F., et al., 2011. Centrality of striatal cholinergic transmission in basal ganglia function [internet]. Front. Neuroanat. 5, 6.
Breakefield, X.O., Kamm, C., Hanson, P.I., 2001. TorsinA: movement at many levels. Neuron 31 (1), 9–12.
Breakefield, X.O., Blood, A.J., Li, Y., Hallett, M., Hanson, P.I., Standaert, D.G., 2008. The pathophysiological basis of dystonias. Nat. Rev. Neurosci. 9, 222.
Bressman, S.B., Raymond, D., Wendt, K., Saunders–Pullman, R., de Leon, D., Fahn, S., et al., 2002 Dec 10. Diagnostic criteria for dystonia in DYT1 families. Neurology 59 (11), 1780 LP–1782.
Brockmann, K., Srulijes, K., Hauser, A.-K., Schulte, C., Csoti, I., Gasser, T., et al., 2011. GBA-associated PD presents with nonmotor characteristics. Neurology 77 (3), 276 LP–280.
Brockmann, K., Srulijes, K., Pflederer, S., Hauser, A.-K., Schulte, C., Maetzler, W., et al., 2014. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov. Disord. 30 (3), 407–411.
Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., Di Lazzaro, V., 2001. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J. Neurosci. 21 (3), 1033 LP–1038.
Calabresi, P., Picconi, B., Tozzi, A., Ghiglieri, V., Di Filippo, M., 2014. Direct and indirect pathways of basal ganglia: a critical reappraisal. Nat. Neurosci. 17, 1022 .
Calabresi, P., Pisani, A., Rothwell, J., Ghiglieri, V., Obeso, J.A., Picconi, B., 2016. Hyperkinetic disorders and loss of synaptic downscaling. Nat. Neurosci. 19, 868 .
Cannas, A., Solla, P., Floris, G., Tacconi, P., Serra, A., Piga, M., et al., 2009. Reversible Pisa syndrome in patients with Parkinson's disease on dopaminergic therapy. J. Neurol. 256 (3), 390–395.
Carella, F., Giovannini, P., Girotti, F., Testa, D., Caraceni, T., 1993. Dystonia and Parkinson's disease. Internet. Adv. Neurol. 60, 558–561.
Castro Caldas, A., Correia Guedes, L., Ferreira, J.J., Coelho, M., 2016 Jun 6. Musician's dystonia as the initial presentation of Parkinson's disease. Mov. Disord. Clin. Pract. 3 (6), 624–625.
Centonze, D., Gubellini, P., Picconi, B., Calabresi, P., Giacomini, P., Bernardi, G., 1999. Unilateral dopamine denervation blocks corticostriatal LTP. J. Neurophysiol. 82 (6), 3575–3579.
Ceravolo, R., Nicoletti, V., Garavaglia, B., Reale, C., Kiferle, L., Bonuccelli, U., 2013. Expanding the clinical phenotype of DYT5 mutations: is multiple system atrophy a possible one? Neurology 81 (3), 301 LP–302.
Chan, A.Y., Chan, A., Lau, D., Durcanova, B., Miller, C.A., Larson, P.S., et al., 2018. Surgical management of camptocormia in Parkinson's disease: systematic review and meta-analysis. J. Neurosurg. 1–5.
Chang, F.C.F., Josephs, K.A., 2013 Apr 18. Levodopa responsiveness in adult-onset lower limb dystonia is associated with the development of Parkinson's disease. Tremor Other Hyperkinet. Mov. (N Y) 3 . (tre-03-150-3598-2).
Charcot, J., 1877. Lectures on the Diseases of the Nervous System, Lecture V. London New Sydenham Soc.
Chase, T.N., Oh, J.D., 2000. Striatal mechanisms and pathogenesis of parkinsonian signs and motor complications. Ann. Neurol. 47 (4 Suppl 1), S122–S129 2000/04/13. (discussion S129-30).
Chiken, S., Nambu, A., 2015. Mechanism of deep brain stimulation: inhibition, excitation, or disruption? Neurosci 22 (3), 313–322.
Chu Chen, C., Kühn, A.A., Trottenberg, T., Kupsch, A., Schneider, G.-H., Brown, P., 2006. Neuronal activity in globus pallidus interna can be synchronized to local field potential activity over 3–12 Hz in patients with dystonia. Exp. Neurol. 202 (2), 480–486.
Cordivari, C., Misra, V.P., Catania, S., Lees, A.J., 2001. Treatment of dystonic clenched fist with botulinum toxin. Mov. Disord. 16 (5), 907–913.
Crittenden, J.R., Tillberg, P.W., Riad, M.H., Shima, Y., Gerfen, C.R., Curry, J., et al., 2016 Oct 4. Striosome–dendron bouquets highlight a unique striatonigral circuit targeting dopamine-containing neurons. Proc. Natl. Acad. Sci. 113 (40), 11318 LP–11323.
Dang, M.T., Yokoi, F., Cheetham, C.C., Lu, J., Vo, V., Lovinger, D.M., et al., 2012 Jan 15. An anticholinergic reverses motor control and corticostriatal LTD deficits in Dyt1 ΔGAG knock-in mice. Behav. Brain Res. 226 (2), 465–472 2011/10/08.
de Schipper, L.J., Boon, A.J.W., Munts, A.G., 2015. Foot drop dystonia resulting from *parkin* (PARK2) mutation. Mov. Disord. Clin. Pract. 2 (3), 292–294.
Denny-Brown, D., 1962. The Basal Ganglia and their Relation to Disorders of Movement. Clarendon Press, London.
Denny-Brown, D., 1968. Clinical symptomatology of diseases of the basal ganglia. Handb. Clin. Neurol. 6, 133–172.
Desban, M., Kemel, M.L., Glowinski, J., Gauchy, C., 1993. Spatial organization of patch and matrix compartments in the rat striatum. Neuroscience 57 (3), 661–671.
Djaldetti, R., Mosberg-Galili, R., Sroka, H., Merims, D., Melamed, E., 2001 Jan 23. Camptocormia (bent spine) in patients with Parkinson's disease—characterization and possible pathogenesis of an unusual phenomenon. Mov. Disord. 14 (3), 443–447.
Doherty, K.M., van de Warrenburg, B.P., Peralta, M.C., Silveira-Moriyama, L., Azulay, J.-P., Gershanik, O.S., et al., 2011. Postural deformities in Parkinson's disease. Lancet Neurol. 10 (6), 538–549.
Dohm, C.P., Gröschel, S., Liman, J., Bähr, M., Kermer, P., 2013. Dropped head sign induced by transdermal application of the dopamine agonist rotigotine in parkinsonian syndrome: a case report. J. Med. Case Rep. 7, 174 .
Duvoisin, R.C., Marsden, C.D., 1975. Note on the scoliosis of parkinsonism. J. Neurol. Neurosurg. Psychiatry 38 (8), 787–793.
Ekbom, K., Lindholm, H., Ljungberg, L., 1972. New dystonic syndrome associated with butyrophenone therapy. Z. Neurol. 202 (2), 94–103.
Elia, A.E., Del Sorbo, F., Romito, L.M., Barzaghi, C., Garavaglia, B., Albanese, A., 2014. Isolated limb dystonia as presenting feature of Parkin disease. J. Neurol. Neurosurg. Psychiatry 85 (7), 827–828.
Erro, R., Stamelou, M., Ganos, C., Skorvanek, M., Han, V., Batla, A., et al., 2014. The clinical syndrome of paroxysmal exercise-induced dystonia: diagnostic outcomes and an algorithm. Mov. Disord. Clin. Pract. 1 (1), 57–61.
Foffani, G., Priori, A., Egidi, M., Rampini, P., Tamma, F., Caputo, E., et al., 2003. 300-Hz subthalamic oscillations in Parkinson's disease. Brain 126 (10), 2153–2163.
Fujimoto, K., 2006. Dropped head in Parkinson's disease. J. Neurol. 253 (7), vii21–vii26.
Furukawa, Y., Kish, S.J., 2015. Parkinsonism in GTP cyclohydrolase 1-deficient DOPA-responsive dystonia. Brain 138 (5), e351.
Furukawa, Y., Nygaard, T.G., Gütlich, M., Rajput, A.H., Pifl, C., DiStefano, L., et al., 1999 Sep 1. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. Neurology 53 (5), 1032 LP–1032.
Fuß, G., Spiegel, J., Magnus, T., Moringlane, J.R., Becker, G., Dillmann, U., 2004. Improvement of apraxia of lid opening by STN-stimulation in a 70-year-old patient with Parkinson's disease. Minim. Invasive Neurosurg. 47 (01), 58–60.
Giasson, B.I., Duda, J.E., Murray, I.V.J., Chen, Q., Souza, J.M., Hurtig, H.I., et al., 2000 Nov 3. Oxidative damage linked to neurodegeneration by selective α-synuclein nitration in synucleinopathy lesions. Science (80-) 290 (5493), 985 LP–989.
Giladi, N., Meer, J., Honigman, S., 1994. The use of botulinum toxin to treat “striatal” toes. J. Neurol. Neurosurg. Psychiatry 57 (5), 659.
Gortvai, P., 1963. Deformities of the hands and feet in parkinsonism and their reversibility by operation. J. Neurol. Neurosurg. Psychiatry 26 (1), 33–36.
Goto, S., Lee, L.V., Munoz, E.L., Tooyama, I., Tamiya, G., Makino, S., et al., 2005 Jul 1. Functional anatomy of the basal ganglia in X-linked recessive dystonia-parkinsonism. Ann. Neurol. 58 (1), 7–17.
Grimes, J.D., Hassan, M.N., Trent, G., Halle, D., Armstrong, G.W., 1987. Clinical and radiographic features of scoliosis in Parkinson's disease. Adv. Neurol. 45, 353–355.
Guduru, Z., Morgan, J., Sethi, K.D., 2017. Anterocollis as an “off” phenomenon in Parkinson disease. Mov. Disord. Clin. Pract. 4 (6), 901–902.
Guella, I., Sherman, H.E., Appel-Cresswell, S., Rajput, A., Rajput, A.H., Farrer, M.J., 2015 May. Parkinsonism in GTP cyclohydrolase 1 mutation carriers. Brain 138 (Pt 5), e349.
Hartmann, A., Pogarell, O., Oertel, W.H., 1998. Secondary dystonias. J. Neurol. 245 (8), 511–518.
Healy, D.G., Falchi, M., O'Sullivan, S.S., Bonifati, V., Durr, A., Bressman, S., et al., 2008a. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 7 (7), 583–590.
Healy, D.G., Wood, N.W., Schapira, A.H.V., 2008b. Test for LRRK2 mutations in patients with Parkinson's disease. Pract. Neurol. 8 (6), 381–385.
Hoffmann, G.F., Assmann, B., Bräutigam, C., Dionisi-Vici, C., Häussler, M., de Klerk, J.B.C., et al., 2003. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann. Neurol. 54 (S6), S56–S65.
Hu, M.T.M., Bland, J., Clough, C., Ellis, C.M., Chaudhuri, K.R., 1999. Limb contractures in

levodopa-responsive parkinsonism. J. Neurol. 246 (8), 671–676.
Ishikawa, A., Miyatake, T., 2018. A family with hereditary juvenile dystonia-parkinsonism. Mov. Disord. 10 (4), 482–488.
Jankovic, J., 2004. Botulinum toxin in clinical practice. J. Neurol. Neurosurg. Psychiatry 75 (7), 951 LP–957 .
Jankovic, J., 2010. Camptocormia, head drop and other bent spine syndromes: heterogeneous etiology and pathogenesis of parkinsonian deformities. Mov. Disord. 25 (5), 527–528.
Jankovic, J., Tintner, R., 2001. Dystonia and parkinsonism. Parkinsonism Relat. Disord. 8 (2), 109–121.
Jin, S.M., Youle, R.J., 2012. PINK1- and Parkin-mediated mitophagy at a glance. J. Cell Sci. 125 (Pt 4), 795–799.
Jinnah, H.A., Albanese, A., 2014. The new classification system for the dystonias: why was it needed and how was it developed? Mov. Disord. Clin. Pract. 1 (4), 280–284 .
Johnston, J.G., Gerfen, C.R., Haber, S.N., van der Kooy, D., 1990. Mechanisms of striatal pattern formation: conservation of mammalian compartmentalization. Dev. Brain Res. 57 (1), 93–102.
Kaji, R., Bhatia, K., Graybiel, A.M., 2018 May 1. Pathogenesis of dystonia: is it of cerebellar or basal ganglia origin? J. Neurol. Neurosurg. Psychiatry 89 (5), 488 LP–492.
Kane, A., Hutchison, W.D., Hodaie, M., Lozano, A.M., Dostrovsky, J.O., 2009. Dopamine-dependent high-frequency oscillatory activity in thalamus and subthalamic nucleus of patients with Parkinson's disease. Neuroreport 20 (17).
Karkheiran, S., Shahidi, G.A., Walker, R.H., 2015. PLA2G6-associated dystonia-parkinsonism: case report and literature review. Tremor Other Hyperkinet. Mov. 5 (0), 317.
Kashihara, K., Ohno, M., Tomita, S., 2006. Dropped head syndrome in Parkinson's disease. Mov. Disord. 21 (8), 1213–1216.
Kasten, M., Hartmann, C., Hampf, J., Schaake, S., Westenberger, A., Vollstedt, E.-J., et al., 2018. Genotype-phenotype relations for the Parkinson's disease genes Parkin, PINK1, DJ1: MDSGene systematic review. Mov. Disord. 33 (5), 730–741.
Kastner, A., Hirsch, E.C., Agid, Y., Javoy-Agid, F., 1993. Tyrosine hydroxylase protein and messenger RNA in the dopaminergic nigral neurons of patients with Parkinson's disease. Brain Res. 606 (2), 341–345.
Kataoka, H., Ueno, S., 2011. Dropped head associated with amantadine in Parkinson disease. Clin. Neuropharmacol. 34 (1).
Kawahata, I., Ohtaku, S., Tomioka, Y., Ichinose, H., Yamakuni, T., 2015. Dopamine or biopterin deficiency potentiates phosphorylation at 40Ser and ubiquitination of tyrosine hydroxylase to be degraded by the ubiquitin proteasome system. Biochem. Biophys. Res. Commun. 465 (1), 53–58.
Khan, N.L., Graham, E., Critchley, P., Schrag, A.E., Wood, N.W., Lees, A.J., et al., 2003. Parkin disease: a phenotypic study of a large case series. Brain 126 (6), 1279–1292.
Kidron, D., Melamed, E., 1987 Jun. Forms of dystonia in patients with Parkinson's disease. Neurology 37 (6), 1009–1011.
Kiely, A.P., Ling, H., Asi, Y.T., Kara, E., Proukakis, C., Schapira, A.H., et al., 2015. Distinct clinical and neuropathological features of G51D SNCA mutation cases compared with SNCA duplication and H50Q mutation. Mol. Neurodegener. 10, 41.
Klein, C., Löchte, T., Delamonte, S.M., Brænne, I., Hicks, A.A., Zschiedrich-Jansen, K., et al., 2016. PLA2G6 mutations and parkinsonism: long-term follow-up of clinical features and neuropathology. Mov. Disord. 31 (12), 1927–1929.
Konno, T., Ross, O.A., Puschmann, A., Dickson, D.W., Wszolek, Z.K., 2016. Autosomal dominant Parkinson's disease caused by SNCA duplications. Parkinsonism Relat. Disord. 22 (Suppl 1), S1–S6.
Krack, P., Pollak, P., Limousin, P., Hoffmann, D., Benazzouz, A., Le Bas, J.F., et al., 1998. Opposite motor effects of pallidal stimulation in Parkinson's disease. Ann. Neurol. 43 (2), 180–192.
Kühn, A.A., Tsui, A., Aziz, T., Ray, N., Brücke, C., Kupsch, A., et al., 2009. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp. Neurol. 215 (2), 380–387.
Kurian, M.A., Morgan, N.V., MacPherson, L., Foster, K., Peake, D., Gupta, R., et al., 2008. Phenotypic spectrum of neurodegeneration associated with mutations in the PLA2G6 gene (PLAN). Neurology 70 (18), 1623 LP–1629.
Kyriakides, T., Hewer, R.L., 1988 Sep. Hand contractures in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 51 (9), 1221–1223.
Laroche, M., Cintas, P., 2010. Bent spine syndrome (camptocormia): a retrospective study of 63 patients. Jt. Bone Spine 77 (6), 593–596.
Lepoutre, A.-C., Devos, D., Blanchard-Dauphin, A., Pardessus, V., Maurage, C.-A., Ferriby, D., et al., 2006 Nov. A specific clinical pattern of camptocormia in Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 77 (11), 1229–1234.
Leung, J.C.O., Klein, C., Friedman, J., Vieregge, P., Jacobs, H., Doheny, D., et al., 2001. Novel mutation in the TOR1A [DYT1] gene in atypical, early onset dystonia and polymorphisms in dystonia and early onset parkinsonism. Neurogenetics 3 (3), 133–143.
LeWitt, P.A., Burns, R.S., Newman, R.P., 1986. Dystonia in untreated parkinsonism. Clin. Neuropharmacol. 9 (3), 293–297 1986/01/01.
Lewthwaite, A.J., Lambert, T.D., Rolfe, E.B., Olgiati, S., Quadri, M., Simons, E.J., et al., 2015. Novel GCH1 variant in Dopa-responsive dystonia and Parkinson's disease. Parkinsonism Relat. Disord. 21 (4), 394–397.
Li, X., Lee, J., Parsons, D., Janaurajs, K., Standaert, D.G., 2012 Nov 21. Evaluation of TorsinA as a target for Parkinson disease therapy in mouse models. PLoS ONE 7 (11), e50063.
Lüdecke, B., Knappskog, P.M., Clayton, P.T., Surtees, R.A.H., Clelland, J.D., Heales, S.J.R., et al., 1996. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205p) in the tyrosine hydroxylase gene. Hum. Mol. Genet. 5 (7), 1023–1028.
Lundblad, M., Picconi, B., Lindgren, H., Cenci, M.A., 2004. A model of l-DOPA-induced dyskinesia in 6-hydroxydopamine lesioned mice: relation to motor and cellular parameters of nigrostriatal function. Neurobiol. Dis. 16 (1), 110–123.
MacFarlane, D.G., Dieppe, P.A., 1983. Pseudo-rheumatoid deformity in elderly osteoarthritic hands. J. Rheumatol. 10 (3), 489–490 1983/06/01.
Mano, T., 2018. Camptocormia induced by a dopaminergic agonist. Clin. Neuropharmacol. 41 (2), 70–72.
Margraf, N.G., Wrede, A., Rohr, A., Schulz-Schaeffer, W.J., Raethjen, J., Eymess, A., et al., 2010. Camptocormia in idiopathic Parkinson's disease: a focal myopathy of the paravertebral muscles. Mov. Disord. 25 (5), 542–551 Internet. Apr 21.
Mark, M.H., Sage, J.I., Dickson, D.W., Heikkila, R.E., Manzino, L., Schwarz, K.O., et al., 1994. Meige syndrome in the spectrum of Lewy body disease. Neurology 44 (8), 1432–1436 1994/08/01.
Marras, C., Lang, A., van de Warrenburg, B.P., Sue, C.M., Tabrizi, S.J., Bertram, L., et al., 2016. Nomenclature of genetic movement disorders: recommendations of the international Parkinson and movement disorder society task force. Mov. Disord. 31 (4), 436–457.
Melamed, E., 1979 May 1. Early-morning dystonia: a late side effect of long-term levodopa therapy in parkinson's disease. Arch. Neurol. 36 (5), 308–310.
Mencacci, N.E., Isaias, I.U., Reich, M.M., Ganos, C., Plagnol, V., Polke, J.M., et al., 2014. Parkinson's disease in GTP cyclohydrolase 1 mutation carriers. Brain 137 (9), 2480–2492.
Miki, Y., Yoshizawa, T., Morohashi, S., Seino, Y., Kijima, H., Shoji, M., et al., 2017. Neuropathology of PARK14 is identical to idiopathic Parkinson's disease. Mov. Disord. 32 (5), 799–800.
Moore, T.J., Evans, W., Murray, D., 1998. Operative management of foot and ankle equinovarus associated with focal dystonia. Foot Ankle Int. 19 (4), 229–231.
Morishita, T., Katayama, Y., Kobayashi, K., Oshima, H., Fukaya, C., Yamamoto, T., 2008. Effect of subthalamic nucleus stimulation on severe striatal hand deformity in Parkinson's disease: a case report. Neuromodulation Technol. Neural Interface 11 (2), 124–127.
Nalls, M.A., Pankratz, N., Lill, C.M., Do, C.B., Hernandez, D.G., Saad, M., et al., 2014 Sep. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat. Genet. 46 (9), 989–993.
Nambu, A., Tachibana, Y., Chiken, S., 2015. Cause of parkinsonian symptoms: firing rate, firing pattern or dynamic activity changes? Basal Ganglia 5 (1), 1–6.
Nausieda, P.A., Weiner, W.J., Klawans, H.L., 1980. Dystonic foot response of parkinsonism. Arch. Neurol. 37 (3), 132–136.
Neumann, W.-J., Horn, A., Ewert, S., Huebl, J., Brücke, C., Slentz, C., et al., 2017. A localized pallidal physiomarker in cervical dystonia. Ann. Neurol. 82 (6), 912–924.
Oczkowska, A., Kozubski, W., Lianeri, M., Dorszewska, J., 2013 Dec. Mutations in PRKN and SNCA genes important for the progress of Parkinson's disease. Curr. Genomics 14 (8), 502–517.
Ozelius, L., Kramer, P.L., Moskowitz, C.B., Kwiatkowski, D.J., Brin, M.F., Bressman, S.B., et al., 1989. Human gene for torsion dystonia located on chromosome 9q32-q34. Neuron 2 (5), 1427–1434.
Ozelius, L.J., Hewett, J.W., Page, C.E., Bressman, S.B., Kramer, P.L., Shalish, C., et al., 1997. The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. Nat. Genet. 17 (1), 40–48.
Paisan-Ruiz, C., Bhatia, K.P., Li, A., Hernandez, D., Davis, M., Wood, N.W., et al., 2009. Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann. Neurol. 65 (1), 19–23.
Paisán-Ruiz, C., Li, A., Schneider, S.A., Holton, J.L., Johnson, R., Kidd, D., et al., 2012. Widespread Lewy body and tau accumulation in childhood and adult onset dystonia-parkinsonism cases with PLA2G6 mutations. Neurobiol. Aging 33 (4), 814–823.
Papapetropoulos, S., Singer, C., 2006. Cervical dystonia as a presenting symptom of Parkinson's disease. Parkinsonism Relat. Disord. 12 (8), 514–516.
Perlmutter, J.S., Tempel, L.W., Black, K.J., Parkinson, D., Todd, R.D., 1997 Nov 1. MPTP induces dystonia and parkinsonism. Neurol. Int. 49 (5), 1432 LP–1438.
Phukan, J., Albanese, A., Gasser, T., Warner, T., 2011. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. Lancet Neurol. 10 (12), 1074–1085.
Pisani, A., Bernardi, G., Ding, J., Surmeier, D.J., 2007. Re-emergence of striatal cholinergic interneurons in movement disorders. Trends Neurosci. 30 (10), 545–553.
Poewe, W.H., Lees, A.J., Stern, G.M., 2018. Dystonia in parkinson's disease: clinical and pharmacological features. Ann. Neurol. 23 (1), 73–78.
Poston, K.L., Eidelberg, D., 2012 Oct 1. Functional brain networks and abnormal connectivity in the movement disorders. Neuroimage 62 (4), 2261–2270.
Prakash, K.M., Lang, A.E., 2007. Reversible dopamine agonist induced anterocollis in a multiple system atrophy patient. Mov. Disord. 22 (15), 2292–2293.
Purves-Stewart, 1898. Paralysis agitans, with an account of a new symptom. Lancet 2, 1258–1260.
Quinn, N., 1989. Disproportionate antecollis in multiple system atrophy. Lancet 333 (8642), 844.
Quinn, N.P., 1993. Parkinsonism and dystonia, pseudo-parkinsonism and pseudodystonia. Adv. Neurol. 60, 540–543.
Quinn, N.P., Ring, H., Honavar, M., Marsden, C.D., 1988. Contractures of the extremities in parkinsonian subjects: a report of three cases with a possible association with bromocriptine treatment. Clin. Neuropharmacol. 11 (3), 268–277 1988/06/01.
Rajput, A.H., Gibb, W.R.G., Zhong, X.H., Shannak, K.S., Kish, S., Chang, L.G., et al., 2018. Dopa-responsive dystonia: pathological and biochemical observations in a case. Ann. Neurol. 35 (4), 396–402.
Rana, A.-Q., Kabir, A., Dogu, O., Patel, A., Khondker, S., 2012. Prevalence of blepharospasm and apraxia of eyelid opening in patients with parkinsonism, cervical dystonia and essential tremor. Eur. Neurol. 68 (5), 318–321.
Ray, N.J., Jenkinson, N., Wang, S., Holland, P., Brittain, J.S., Joint, C., et al., 2008. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. Exp. Neurol. 213 (1), 108–113.

Reynolds, F.W., Petropoulous, G.C., 1965. Hand deformities in parkinsonism. J. Chronic Dis. 18 (6), 593–595.
Ryan, S.D., Dolatabadi, N., Chan, S.F., Zhang, X., Akhtar, M.W., Parker, J., et al., 2013. Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1α transcription. Cell 155 (6), 1351–1364.
Sako, W., Nishio, M., Maruo, T., Shimazu, H., Matsuzaki, K., Tamura, T., et al., 2009. Subthalamic nucleus deep brain stimulation for camptocormia associated with Parkinson's disease. Mov. Disord. 24 (7), 1076–1079.
Sato, K., Sumi-Ichinose, C., Kaji, R., Ikemoto, K., Nomura, T., Nagatsu, I., et al., 2008 Aug 26. Differential involvement of striosome and matrix dopamine systems in a transgenic model of dopa-responsive dystonia. Proc. Natl. Acad. Sci. 105 (34), 12551 LP–12556.
Schneider, S.A., Edwards, M.J., Grill, S.E., Goldstein, S., Kanchana, S., Quinn, N.P., et al., 2006 Jun 6. Adult-onset primary lower limb dystonia. Mov. Disord. 21 (6), 767–771.
Schneider, S.A., Bhatia, K.P., Hardy, J., 2009. Complicated recessive dystonia parkinsonism syndromes. Mov. Disord. 24 (4), 490–499.
Schreglmann, S., Burke, D., Batla, A., Kresojevic, N., Wood, N., Heales, S., Bhatia, K., 2018. Decreased blood beta-glucosidase activity and GBA mutations in dystonia. Mov. Disord. 33 (Suppl. 2).
Serratrice, G., Schiano, A., 1976. Scoliosis in Patients with Parkinsonism. vol. 5. La Nouvelle presse medicale, France, pp. 1834.
Sharma, N., Hewett, J., Ozelius, L.J., Ramesh, V., McLean, P.J., Breakefield, X.O., et al., 2001. A close association of TorsinA and alpha-synuclein in Lewy bodies: a fluorescence resonance energy transfer study. Am. J. Pathol. 159 (1), 339–344.
Shashidharan, P., Good, P.F., Hsu, A., Perl, D.P., Brin, M.F., Olanow, C.W., 2000. TorsinA accumulation in Lewy bodies in sporadic Parkinson's disease. Brain Res. 877 (2), 379–381.
Silberstein, P., Kühn, A.A., Kupsch, A., Trottenberg, T., Krauss, J.K., Wöhrle, J.C., et al., 2003. Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. Brain 126 (12), 2597–2608.
Smith, K., Alawi, A., Ramiro, J., Chand, P., 2014 Apr 8. Pronounced task specific writing tremor in Parkinson's disease (P3.079). Neurol. Int. 82 (10 Supplement).
Spanaki, C., Zafeiris, S., Plaitakis, A., 2010. Levodopa-aggravated lateral flexion of the neck and trunk as a delayed phenomenon of unilateral pallidotomy. Mov. Disord. 25 (5), 655–656.
Spuler, S., Krug, H., Klein, C., Medialdea, I.C., Jakob, W., Ebersbach, G., et al., 2010. Myopathy causing camptocormia in idiopathic Parkinson's disease: a multidisciplinary approach. Mov. Disord. 25 (5), 552–559.
Stamelou, M., Mencacci, N.E., Cordivari, C., Batla, A., Wood, N.W., Houlden, H., et al., 2012. Myoclonus-dystonia syndrome due to tyrosine hydroxylase deficiency. Neurology 79 (5), 435 LP–441.
Standaert, D.G., 2011. Update on the pathology of dystonia. Neurobiol. Dis. 42 (2), 148–151.
Strecker, K., Meixensberger, J., Schwarz, J., Winkler, D., 2008. Increase of frequency in Deep Brain Stimulation relieves apraxia of eyelid opening in patients with Parkinson's Disease. Case report. Neurosurgery 63, E1204.
Swaans, R.J., Rondot, P., Renier, W.O., van den Heuvel, L.P., Steenbergen-Spanjers, G.C., Wevers, R.A., 2000. Four novel mutations in the Tyrosine Hydroxylase gene in patients with infantile parkinsonism. Ann. Hum. Genet. 64 (1), 25–31.
Tabamo, R.E.J., Fernandez, H.H., Friedman, J.H., Simon, D.K., 2000. Young-onset Parkinson's disease: a clinical pathologic description of two siblings. Mov. Disord. 15 (4), 744–746.
Taguchi, Y., Takashima, S., Tanaka, K., 2008. Pramipexole-induced dropped head syndrome in Parkinson's disease. Intern. Med. 47 (22), 2011–2012.
Taipa, R., Pereira, C., Reis, I., Alonso, I., Bastos-Lima, A., Melo-Pires, M., et al., 2016. DJ-1 linked parkinsonism (PARK7) is associated with Lewy body pathology. Brain 139 (6), 1680–1687.
Tiple, D., Fabbrini, G., Colosimo, C., Ottaviani, D., Camerota, F., Defazio, G., et al., 2009 Feb 1. Camptocormia in Parkinson disease: an epidemiological and clinical study. J. Neurol. Neurosurg. Psychiatry 80 (2), 145 LP–148.
Tolosa, E., Compta, Y., 2006. Dystonia in Parkinson's disease. J. Neurol. 253 (7), vii7–vii13.
Tommasi, G., Krack, P., Fraix, V., Pollak, P., 2012. Effects of varying subthalamic nucleus stimulation on apraxia of lid opening in Parkinson's disease. J. Neurol. 259 (9), 1944–1950.
Trinh, J., Zeldenrust, F.M.J., Huang, J., Kasten, M., Schaake, S., Petkovic, S., et al., 2018. Genotype-Phenotype Relations for the Parkinson's Disease Genes SNCA, LRRK2, VPS35: MDSGene Systematic Review. pp. 1–14.
Umemura, A., Toyoda, T., Yamamoto, K., Oka, Y., Ishii, F., Yamada, K., 2008. Apraxia of eyelid opening after subthalamic deep brain stimulation may be caused by reduction of levodopa. Parkinsonism Relat. Disord. 14 (8), 655–657.
Umemura, A., Oka, Y., Ohkita, K., Yamawaki, T., Yamada, K., 2010. Effect of subthalamic deep brain stimulation on postural abnormality in Parkinson disease. J. Neurosurg. 112 (6), 1283–1288 2009/11/10.
Umemura, A., Oka, Y., Yamamoto, K., Okita, K., Mastsukawa, N., Yamada, K., 2011. Complications of subthalamic nucleus stimulation in Parkinson's disease. Neurol. Med. Chir. (Tokyo) 51 (11), 749–755.
van de Warrenburg, B.P.C., Cordivari, C., Ryan, A.M., Phadke, R., Holton, J.L., Bhatia, K.P., et al., 2007a. The phenomenon of disproportionate antecollis in Parkinson's disease and multiple system atrophy. Mov. Disord. 22 (16), 2325–2331.
van de Warrenburg, B.P.C., Bhatia, K.P., Quinn, N.P., 2007b. Pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event? J. Neurol. Neurosurg. Psychiatry 78 (3), 329–330.
van de Warrenburg, B.P.C., Bhatia, K.P., Quinn, N.P., 2008. Correction to: pisa syndrome after unilateral pallidotomy in Parkinson's disease: an unrecognised, delayed adverse event? J Neurol Neurosurg Psychiatry 2007;78:329–330. J. Neurol. Neurosurg. Psychiatry 79, 337.
van Duijn, C.M., Dekker, M.C., Bonifati, V., Galjaard, R.J., Houwing-Duistermaat, J.J., Snijders, P.J., et al., 2001 Sep. Park7, a novel locus for autosomal recessive early-onset parkinsonism, on chromosome 1p36. Am. J. Hum. Genet. 69 (3), 629–634.
Vilariño-Güell, C., Rajput, A., Milnerwood, A.J., Shah, B., Szu-Tu, C., Trinh, J., et al., 2014. DNAJC13 mutations in Parkinson disease. Hum. Mol. Genet. 23 (7), 1794–1801 Internet. Apr 1.
Villarejo, A., Camacho, A., García–Ramos, R., Moreno, T., Penas, M., Juntas, R., et al., 2003. Cholinergic–dopaminergic imbalance in Pisa syndrome. Clin. Neuropharmacol. 26 (3).
Vitek, J.L., 2008. Deep brain stimulation: how does it work? Cleve. Clin. J. Med. 75 (Suppl. 2), S59–S65 2008/06/11.
von Coelln, R., Raible, A., Gasser, T., Asmus, F., 2008. Ultrasound-guided injection of the iliopsoas muscle with botulinum toxin in camptocormia. Mov. Disord. 23 (6), 889–892.
Wadia, P.M., Tan, G., Munhoz, R.P., Fox, S.H., Lewis, S.J., Lang, A.E., 2011 Apr 1. Surgical correction of kyphosis in patients with camptocormia due to Parkinson's disease: a retrospective evaluation. J. Neurol. Neurosurg. Psychiatry 82 (4), 364 LP–368.
Weinberger, M., Mahant, N., Hutchison, W.D., Lozano, A.M., Moro, E., Hodaie, M., et al., 2006. Beta oscillatory activity in the subthalamic nucleus and its relation to dopaminergic response in Parkinson's disease. J. Neurophysiol. 96 (6), 3248–3256.
Weinberger, M., Hutchison, W.D., Alavi, M., Hodaie, M., Lozano, A.M., Moro, E., et al., 2012. Oscillatory activity in the globus pallidus internus: comparison between Parkinson's disease and dystonia. Clin. Neurophysiol. 123 (2), 358–368.
Wickremaratchi, M.M., Knipe, M.D.W., Sastry, B.S.D., Morgan, E., Jones, A., Salmon, R., et al., 2011. The motor phenotype of Parkinson's disease in relation to age at onset. Mov. Disord. 26 (3), 457–463.
Wider, C., Skipper, L., Solida, A., Brown, L., Farrer, M., Dickson, D., et al., 2008. Autosomal dominant dopa-responsive parkinsonism in a multigenerational Swiss family. Parkinsonism Relat. Disord. 14 (6), 465–470.
Wijemanne, S., Jankovic, J., 2015. Dopa-responsive dystonia—clinical and genetic heterogeneity. Nat. Rev. Neurol. 11, 414.
Winkler, A.S., Reuter, I., Harwood, G., Chaudhuri, K.R., 2002. The frequency and significance of striatal toe in parkinsonism. Parkinsonism Relat. Disord. 9 (2), 97–101.
Yang, J.-F., Wu, T., Li, J.-Y., Li, Y.-J., Zhang, Y.-L., Chan, P., 2009. DYT1 mutations in early onset primary torsion dystonia and Parkinson disease patients in Chinese populations. Neurosci. Lett. 450 (2), 117–121.
Yoon, W.T., Chung, E.J., Lee, S.H., Kim, B.J., Lee, W.Y., 2005. Clinical analysis of blepharospasm and apraxia of eyelid opening in patients with parkinsonism. J. Clin. Neurol. 1 (2), 159–165.
Zauber, S.E., Watson, N., Comella, C.L., Bakay, R.A.E., Metman, L.V., 2009. Stimulation-induced parkinsonism after posteroventral deep brain stimulation of the globus pallidus internus for craniocervical dystonia. J. Neurosurg. JNS 110 (2), 229–233.