Parkinsonism and dystonia: clinical spectrum and diagnostic clues

Hugo Morales-Briceno, MD [1, 2], Victor SC Fung PhD, FRACP [1, 2], Kailash P Bhatia FRCP [3], Bettina Balint MD [4]

1 Neurology Department, Movement Disorders Unit, Westmead Hospital, NSW, Sydney, Australia
2 Sydney Medical School, University of Sydney, Sydney, NSW 2145, Australia
3 UCL Queen Square Institute of Neurology Department of Clinical and Movement Neurosciences, Queen Square, London WC1N 3BG, United Kingdom
4 Department of Neurology, University Hospital Heidelberg, Germany

Corresponding author:
Dr Bettina Balint
Department of Neurology
University Hospital Heidelberg
69120 Heidelberg
Germany
Email: dr.bettina.balint@gmail.com
Telephone: +49 6221 5632631

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Abstract

The links between the two archetypical basal ganglia disorders, dystonia and parkinsonism, are manifold and stem from clinical observations, imaging studies, animal models and genetics. The combination of both, i.e the syndrome of dystonia-parkinsonism, is not uncommonly seen in movement disorders clinics and has a myriad of different underlying aetiologies, upon which treatment and prognosis depend. Based on a comprehensive literature review, we delineate the clinical spectrum of disorders presenting with dystonia-parkinsonism. The clinical approach depends primarily on the age at onset, associated neurological or systemic symptoms and neuroimaging. The tempo of disease progression, and the response to L-dopa are further important clues to tailor diagnostic approaches that may encompass dopamine transporter imaging, CSF analysis and, last but not least, genetic testing. Later in life, sporadic neurodegenerative conditions are the most frequent cause, but the younger the patient, the more likely the cause is unravelled by the recent advances of

molecular genetics that are focus of this review. Here, knowledge of the associated phenotypic spectrum is key to guide genetic testing and interpretation of test results.

Introduction

Dystonia and parkinsonism are two distinct syndromes with a remarkable degree of aetiological and clinical heterogeneity.[1] Both conditions can develop after similar focal lesions in the basal ganglia circuits or in a hypodopaminergic state, suggesting a pathophysiological overlap between these movement disorders (*see box*). Nevertheless, the underlying pathophysiological underpinnings that account for dystonia and parkinsonism in patients presenting with this syndrome remain poorly understood.[2] The syndrome of dystonia-parkinsonism is not uncommonly seen in specialised movement disorders clinics, and particularly its genetic differential diagnosis has become more extensive due to the wider use of molecular diagnostic technologies.

In this review, we performed a literature review to delineate the clinical spectrum of disorders that can present with dystonia-parkinsonism syndrome. We touch upon clues for acquired causes (figure 1) before focusing on the expanding spectrum of hereditary causes.

Definition of the dystonia-parkinsonism

The definition of dystonia-parkinsonism encompasses the combination of dystonia - a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both - *PLUS* parkinsonism defined as bradykinesia, in combination with either rest tremor, rigidity, or both.[3, 4] According to the current MDS classification, dystonia with additional parkinsonian signs is termed combined dystonia or dystonia with parkinsonism.[3, 5] With the aim to capture the full spectrum of the syndrome, we have also included conditions presenting with parkinsonism in which dystonia may be present, either a focal, segmental or generalised distribution.

Search criteria

A literature search was performed in PubMed, without a date limit and up to 20 April 2021. A combination of keywords such dystonia-parkinsonism, parkinsonism-dystonia, dystonia AND Parkinsonism in combination with the following terms: genetic; infectious OR infection;

autoimmune; paraneoplastic; drug induced; tardive; neurodegenerative; toxic; metabolic; vascular was used to identify articles. We aimed to select all relevant identified papers, including reviews, case series, and case reports that refer to dystonia-parkinsonism phenotype. Current classification systems stress the value of clinical descriptors, which can be used to categorise a syndrome. Here we also adopt a similar approach and use a combination of age of onset, distribution of dystonia, response to levodopa, other movement disorders phenomenology, presence of other neurological or extra-neurological features and brain imaging patterns.

Diagnostic approach of the patient with dystonia-parkinsonism

Dystonia-parkinsonism can be the result of structural, metabolic, drug-induced, infectious, autoimmune, and genetic disorders. A detailed description of the phenomenology of the movement disorder is the first step for a correct syndromic diagnosis. Subsequently, the differential diagnostic considerations are orientated by the clinical history (e.g., exposure to drugs, preceding or accompanying symptoms, family history), the age of onset, the tempo of disease and orientated investigations.

In the following, we start with the description of acquired causes of dystonia-parkinsonism and the relevant diagnostic clues (figure 1), to focus then on the genetic disorders and the pertinent approach (figure 2 and 3).

Acquired parkinsonism-dystonia syndromes

Drug-induced dystonia-parkinsonism

Acquired causes of dystonia-parkinsonism encompass potentially treatable conditions. For example, dopamine receptor blocking drugs, including antipsychotics and antiemetics, are a frequent cause of dystonia-parkinsonism, and early recognition is essential to allow for prompt intervention. Dystonia-parkinsonism can develop subacutely, but more commonly after several years of use of these medications. In some cases, parkinsonism may be indistinguishable from idiopathic PD, whereas in others, the co-existence of akathisia, oral-buccal-lingual and tardive dystonia hint at the diagnosis of a drug-induced syndrome. Of note, in those with persistent parkinsonism even after withdrawal of the offending drug, dopamine transporter imaging (DAT scan) can be a key investigation to reveal an underlying

nigrostriatal denervation, pointing towards an underlying neurodegenerative disorder as important differential diagnosis. Lastly, there are occasional reports of dystonia-parkinsonism induced by other medications, such as cyclosporine A and adalimumab, though the underlying mechanisms are unclear [6, 7].

Infectious and autoimmune dystonia-parkinsonism

Dystonia-parkinsonism may develop in patients with infectious encephalitis, in particular in those with basal ganglia lesions, such as Japanese encephalitis, Dengue and West Nile encephalitis; rarer associations, without structural lesions on imaging, have been described e.g. for Epstein Barr virus[8]. Systemic signs like fever or a history of mosquito bites in endemic regions would prompt such differential diagnosis and testing. Very rarely, dystonia-parkinsonism may be a feature of subacute sclerosing panencephalitis, a late sequelae of the primary infection with measles, where Rapidly progressive dementia and periodic myoclonus are major clues to the diagnosis, which can be confirmed by raised measles antibody titres in serum and cerebrospinal fluid (CSF) [9]. Dystonia-parkinsonism may also develop as an autoimmune, post- or parainfectuous syndrome after encephalitis, often without an identifiable antibody. Autoimmune dystonia-parkinsonism syndromes are very rare, but potentially treatable. Here, dystonia-parkinsonism typically occurs subacutely in the context of an encephalopathy with other signs like cognitive or psychiatric disturbance and seizures. Rapid progression of the disease is another red flag. Basal ganglia encephalitis with dopamine-2 receptor antibodies is seen in children [15], while particularly in young women, an unusual manifestation of anti-NMDAR encephalitis needs to be considered.[17, 18, 19] Similarly, subacute onset of dystonia-parkinsonism with a psychiatric disorder in children, adolescence or early adulthood may be a rare manifestation of systemic lupus erythematosus and antiphospholipid syndrome [16]. In adults, (pseudo-)dystonia-parkinsonism phenocopies can be seen with glutamic acid decarboxylase, glycine receptor antibodies, or IgLON5 antibodies, and in paraneoplastic syndromes (e.g. with Ma2 or Ri antibodies or in seronegative cases) [20].

Dystonia-parkinsonism with structural abnormalities

Structural basal ganglia lesions including stroke and tumours are a frequently associated with the syndrome, though lesions at any level between the midbrain and subcortical white matter may cause the syndrome. Delayed presentation of dystonia-parkinsonism due to basal ganglia lesions may occur after osmotic demyelination and methanol or carbon monoxide intoxication [21]. Pallidal lesions are characteristic of carbon monoxide intoxication, whereas putaminal lesions are suggestive of methanol intoxication. In patients with unilateral limbs, face, or trunk atrophy, in combination with contralateral hemispheric atrophy may support the diagnosis of hemiparkinsonim-hemiatrophy syndrome, where accompanying dystonia has been reported [22, 23]. Furthermore, clinicians should be alert to the characteristic imaging features of acquired hepatocerebral degeneration which can manifest as dystonia-parkinsonism. In the T1-sequences there is a bilateral pallidal hyperintensity that reveals manganese deposition. However, in patients without history of chronic hepatic disease, manganese intoxication associated with intravenous administration of ephedrine should be considered in the appropriate context.

Genetic dystonia-parkinsonism

The spectrum of the genetic aetiologies of dystonia-parkinsonism keeps expanding. Because of the differential diagnosis greatly depending on the age of onset, we have grouped those conditions accordingly. For example, monoamine synthesis and dopamine transport disorders often present with dystonia-parkinsonism in childhood (detailed in table 1). In contrast, in early adulthood, syndromes of neurodegeneration with brain iron accumulation (table 2) become an important consideration. Later in life, sporadic neurodegenerative disease and its genetic mimics come to the fore. Apart from age, the differential diagnosis is also guided by the presence or absence of neuroimaging abnormalities (figure 2 and 3). A list summarizing genetic conditions that often present as dystonia-parkinsonism syndrome is provided in table 3, while rarer condition that may present with dystonia-parkinsonism are listed in the supplementary table.

Genetic dystonia-parkinsonism with childhood and adolescence onset (<20 years)

The syndrome of dystonia-parkinsonism can occur as early as in the infantile period to childhood and adolescence. The evaluation of these patients should be focused on treatable and potentially reversible causes, which mainly include Wilson's disease, neurotransmitter disorders, neurometabolic causes, including, organic acidurias and aminoacidopathies.

Infantile cases can present with a hypokinetic-rigid syndrome, where dystonia, more commonly in a generalised distribution, may be seen in up to 90% of cases.[24] Often, axial hypotonia is one of the first findings, and delayed milestones become noticeable during the disease course.

The most common cause of dystonia-parkinsonism in this age group are disorders of monoamine synthesis and dopamine transport disorders (Table 1). Suggestive features of neurotransmitter deficiency include oculogyric crises, diurnal fluctuation, somnolence, autonomic symptoms (excessive sweating, hypersalivation or temperature instability), ptosis and chorea.[25] In infants, commonly reported genetic causes of dystonia-parkinsonism include TH and DDC deficiency, but other frequent disorders include pathogenic variants in *GCH1*, *SLC18A2*, *SLC6A3* and *SPR*. Single cases of *DHPR*, *PTPS* and *SLC39A14* pathogenic variants have also been reported to cause this syndrome. Although the definitive diagnosis relies on molecular confirmation of a pathogenic variant or cerebrospinal fluid analysis, there are some clinical clues that may suggest a specific disorder: for instance, moderate to excellent response to L-dopa is seen in patients with *GCH1* variants and milder forms of TH deficiency, whereas the response is little or absent in in disorders of monoamine vesicular transport due to *SLC18A2* or *SLC6A3* pathogenic variantss.[24] Exacerbation of dystonia has been reported in these two last disorders, and amelioration of their dystonia-parkinsonism has been observed after dopamine agonist therapy.[26]

In childhood-onset (3-12 years) dystonia-parkinsonism, the number of causative conditions is broader but acquired conditions such as structural lesions, infectious, autoimmune and metabolic disease should be initially considered. Neurotransmitter disorders such as *GCH1* and *TH* can also occur at this age. Brain iron accumulation syndromes (Table 2) can be identified on the basis of their distinctive clinical and imaging features and are a common

cause of dystonia-parkinsonism in childhood.[27] Huntington disease can manifest as dystonia-parkinsonism with a neuropsychiatric syndrome, myoclonus, slow saccades and epilepsy and should be suspected in cases with a family history of the disorder. MRI brain imaging can show caudate atrophy, striatal T2-hyperintensities and iron deposition in the striatum in some cases.[28] Pathogenic variants in *SLC30A10* [29] and *SLC39A14* [30] cause hypermanganesemia and manganese brain accumulation and are potentially treatable with chelation therapy and iron supplementation.[31] The phenotype includes generalised dystonia-parkinsonism with bulbar involvement, anarthria/aphonia, and spasticity with MRI T1-hyperintensities from the pallidum, brainstem tegmentum to the dentate nucleus.[32] High-stepping gait ("cock-walk gait") is suggestive of manganese accumulation.[33]

Genetic early-onset parkinsonism can also have predominant dystonia-parkinsonism presentations. Autosomal dominant or de novo pathogenic variants in *ATP1A3*, now recognised to be a spectrum of disorders, were initially described in patients with rapid-onset dystonia-parkinsonism.[34] The original phenotypic description abrupt onset of dystonia with features of parkinsonism over a few minutes to 30 days, a clear rostrocaudal (face > arm > leg) gradient, and prominent bulbar findings. In a recent systematic evaluation of 50 *ATP1A3* pathogenic variants-positive, a rostrocaudal gradient of severity was only seen in 7%, but a rapid onset was reported in 80% of cases.[35] Bulbar involvement was prominent in 91% of them, but the most common first affected region was the arm. Paroxysmal limb dystonia can be a useful clue to *ATP1A3*.[36-38]

Dystonia-parkinsonism is frequently seen in recessive pathogenic variants causing early-onset parkinsonism. Heterozygous or homozygous *PLA2G6* pathogenic variants present in infancy with progressive neurological regression, hypotonia, loss of ambulation commonly associated with pyramidal signs, neuropathy and cognitive and neuropsychiatric manifestations.[39] Dystonia-parkinsonism is usually a late feature in this context, but it has been reported as the presenting feature. Cerebellar atrophy is a frequent finding, and other imaging clues are pallidal iron deposition, claval hypertrophy and cerebellar cortex hyperintensities.[39] In *ATP13A2*-related disease, the age of onset is ~14 years, and atypical parkinsonism is present in 83% of these cases.[40] Facial-faucial-finger myoclonus, up gaze saccadic palsy, cognitive impairment, pyramidal signs and brain iron accumulation are also part of the syndrome. Dystonia accompanies the parkinsonism in a subset of patients

(~40%), and focal, segmental and generalised distribution can be observed.[40] Likewise, *FBXO7* pathogenic variants lead to atypical parkinsonism in 92% of cases, with frequent (73%) pyramidal signs or spasticity.[40] Dystonia is not a prominent feature in *FBXO7* pathogenic variants, but segmental and generalised dystonia has been described in some cases.[41] Recently, recessive pathogenic variants in *DNAJC6* have been identified as the cause of childhood-onset dystonia-parkinsonism syndrome. Symptoms may begin from infancy to adolescence, with ensuing parkinsonism and dystonia and significant neurological regression with loss of ambulation and early death in some.[42] Additional features of developmental delay and seizures may be present in some patients. Neuroimaging is typically normal but generalised brain atrophy has been reported. Treatment with levodopa and dopamine agonist may offer moderate improvement, but severe fluctuations often prevent further titration.[43] A similar disease progression is seen in juvenile-onset neuronal intranuclear inclusion body disease. Parkinsonism and dystonia can be the presenting syndrome and should be suspected in patients with exquisite levodopa response, severe motor fluctuations, and additional cerebellar and pyramidal signs.[44]

Pathogenic variants in *SYNJ1* have been associated with early-onset epileptic encephalopathy or with early-onset parkinsonism.[45, 46] Patients may develop parkinsonism with rest tremor with variable response to levodopa. Segmental dystonia in the cranial, neck and upper limb has been reported in several patients,[47] and adolescent-onset generalised dystonia-parkinsonism responsive to levodopa has also been reported in two siblings.[48] In some of these patients, childhood-onset seizures can precede the onset of dystonia-parkinsonism and are useful clues.

Dystonia-parkinsonism, due to *PRKRA* pathogenic variants (DYT16), has been reported in few families from Brazil, Italy and Germany.[49-51] The onset is usually <13 years in 70% of cases. Segmental dystonia commonly generalises, to bulbar and axial musculature.[52] Oromandibular dystonia and opisthotonus become prominent, whereas non-levodopa responsive parkinsonism is developed later. Although brain MRI is frequently unremarkable, striatal hyperintensities have been reported in some cases.[53] GM1 type 3 gangliosidosis due to β-galactosidase deficiency frequently present as a dystonia-parkinsonism phenotype with generalised dystonia with prominent bulbar and oromandibular dystonia and facial grimacing. Suggestive features include vertebral bone and hip dysplasia, scoliosis, short

stature and corneal opacities. A posterolateral putaminal T2-hyperintensity with a pattern of pallidal iron deposition on SWI resembling a wishbone has been observed in some cases. Biallelic *VAC14* pathogenic variants have been reported to cause childhood-onset striatonigral degeneration. All patients reported to date have had an onset <13 years, usually at three years. After a normal developmental period, patients start with progressive dystonic gait with rapid generalisation causing dysarthria/anarthria. A subset of patients has increased tone or parkinsonism, and survival to adulthood has been observed. Striatal hyperintensities were observed on T2 or FLAIR in 5 of 9 patients in whom MRI was available in one report and thus are suggestive features. Moreover, SWI hypointensities have also been identified in a subset of these patients. The differential diagnosis of dystonia-parkinsonism with striatal lesions during infancy includes *ADAR1* [54], *SERAC1* [55], *SLC19A3* [56], *POLR3A* [57] and *WARS2* [58] pathogenic variants.

In some developmental disorders, dystonia-parkinsonism may emerge during disease progression. Rett syndrome is an X-linked neurodevelopmental disorder affecting mainly females. Onset is in early childhood with loss of motor skills, especially hand dexterity. Acquired microcephaly, autistic behaviour, epilepsy, cognitive and motor regression are also characteristic. Hand stereotypies and bruxism are distinctive features. Focal and segmental dystonia can be seen, but generalised dystonia has also been reported. Parkinsonism appears with disease progression, and a gradual caudal to rostral pattern have been reported in prospective studies.[59] Dystonia-parkinsonism presentation in adolescent boys with neurodevelopmental delay has been reported.[60] *FOXG1* pathogenic variants have been rarely associated with dystonia-parkinsonism.[61] Other disorders with intellectual disability and parkinsonism that can feature dystonia include *PTRHD1* [62], *ATP6AP2* [63] and *RAB39B* [64].

Recently, autosomal dominant, frequently de novo pathogenic variants in *NR4A2* have been identified in patients with intellectual disability, autism spectrum disorder and levodopa responsive dystonia-parkinsonism.[65, 66] In some cases, epilepsy and paroxysmal dystonia, might also be observed.[67] Likewise, autosomal dominant pathogenic variants in *PPP2R5D* are causative of a neurodevelopmental disorder with infantile hypotonia, moderate intellectual disability, macrocephaly and variable presence of seizures.[68, 69] Four of the 32 cases reported to date, have developed parkinsonism later in adolescence or adulthood, and focal dystonia in some patients with parkinsonism have been reported. De novo *UBTF*

pathogenic variants cause early onset neurodevelopmental delay and regression with accompanying cerebral cortex and white matter degenerative changes.[70] Dystonia, spasticity, ataxia and chorea are frequent, and a subgroup also has limb rigidity.[71] A case presenting with dystonia-parkinsonism during childhood has been recently reported.[72]

Although uncommon, dystonia-parkinsonism syndrome can be seen in diseases that usually present as other phenotypes (Supplementary Table 1). Such is the case for dominant spinocerebellar ataxias type 3 and type 21, where the presence of cerebellar atrophy and familial history should suggest the diagnosis. In ataxia-telangiectasia, dystonia and parkinsonism can become more prevalent with disease progression, but dystonia-parkinsonism as the initial presentation has not been reported. Recessive ataxia due to *COQ8A* pathogenic variants can present with hand dystonia (28%); nevertheless, bradykinesia is observed in 16% of the cases.[73] In hereditary recessive spastic paraplegias type 11 and type 15, patients can present with prominent parkinsonism and segmental dystonia; however, the presence of spasticity and thin corpus callosum are commonly detected to support the diagnosis.[74, 75] Genetic disorders with extra-neurologic involvement, in particular, haemotological abnormalities, such as due to pathogenic variants in *PGK1*, *LYST* and *BTK* should be considered accordingly, as these conditions can also occasionally present with predominant dystonia-parkinsonism.[76-78]

Epileptic encephalopathies due to pathogenic variants in *SCN1A* [79], *TBC1D24* [80], *STXBP1* [81], *FRRS1L* and *DHDDS* [82] may rarely feature dystonia and parkinsonism as part of their phenotype but not as part of the initial presentation. In contrast, Lafora disease [83], Tay-Sachs [84] and *CLN2*-related neuronal ceroid lipofuscinosis [85] presenting with predominant dystonia-parkinsonism, myoclonus and epilepsy have been occasionally described. Similarly, de novo *EIF2AK2* pathogenic variants have been found in patients with a neurodevelopmental syndrome with hypomyelination with frequent cognitive and motor regression after febrile illness or infection. Ataxia, dysarthria, hypotonia, dystonia and parkinsonism have been reported in some individuals.[86]

Genetic dystonia-parkinsonism with early-middle adulthood onset (20-50 years)

The aetiological spectrum of dystonia-parkinsonism during early-middle adulthood differ from those with early-onset, and the pattern of dystonia is less likely to be generalised except for some conditions. Furthermore, despite their unusual occurrence in adulthood, neurotransmitter disorders (especially *GCH1* pathogenic variants) should be considered when the clinical features are suggestive. In such cases, a DAT scan can help to differentiate between such disorders of dopamine synthesis (e.g Segawa disease due to *GCH1* pathogenic variants) from disorders of nigrostriatal degeneration (eg. early onset Parkinson' disease due to *Parkin;* see below).

Adult patients with autosomal recessive *PLA2G6* pathogenic variants can have a predominant dystonia-parkinsonism presentation with frequent cognitive decline, depression, and psychosis.[87-89] Pyramidal signs at the examination are seen in 78% of these cases. Cortical atrophy is seen in 64% and cerebellar atrophy in 21%, but only 9% show iron accumulation.[90] Patients can also present as typical early-onset Parkinson's disease including excellent L-dopa response and development of L-dopa induced dyskinesia. X-linked *TAF1* pathogenic variants occur in Philipino men from the Panay region, but female carriers can also be affected. The onset can be as early as 21 years but usually occurs in adulthood. Craniocervical dystonia is the most common location at onset but then generalises over time, while Parkinsonian features emerge progressively in up to 90% of the cases.[91] A characteristic dystonic gait with phasic knee bending has been reported in some patients with *TAF1* pathogenic variantss.[92]

In early-onset recessive Parkinson's disease, the reported prevalence of dystonia is 18% *Parkin*, and 24% in *DJ1* and 46% in *PINK1*.[93] Although presentations of isolated lower limb dystonia and dopa-responsive dystonia have been reported in *Parkin* [94], a recent study found that frequency of dystonia at onset in *Parkin* pathogenic variants carriers and non-carriers is not different.[95] Pathogenic *DJ1* variants have also been reported in dystonia-parkinsonism with additional, neuropsychiatric and pyramidal features with onset during adolescence.[96] In adults with 22q11.2DS-related parkinsonism, dystonia is not commonly seen [93], however in children isolated mild dystonic posturing is seen in 94% of cases. Nevertheless, there are no cases in the literature with dystonia-parkinsonism presentations.

VPS13A pathogenic variants underlie the syndrome of chorea-acanthocytosis but dystonia and parkinsonism may become more prevalent with disease progression, and very rarely, be

the presenting feature.[84, 8]. The most conspicuous feature is a pattern of orolingual feeding dystonia, where the tongue pushes the food out of the mouth. Chorea and dystonia are the most frequent phenomenology, and obsessive-compulsive spectrum disorders, including tics or tourettism, is seen as well. Areflexia and elevated serum CK are very common. A "stutter-step" gait combined chorea, dystonia and parkinsonism has been described in this disorder. [97] The differential diagnosis of choreic syndromes that can develop dystonia-parkinsonism includes Huntington´s disease and HDL-2. [98]

Mineralisation in neuroimaging is a helpful radiological clue in dystonia-parkinsonism: in patients with neurodegeneration with brain iron accumulation (NBIA) presenting in adulthood,(autosomal recessive) *PANK2*, (autosomal recessive or dominant) *C19ORF12* and (autosomal dominant) *FTL* pathogenic variants should be the main considerations. [27]

The syndrome of primary familial brain calcification (PFBC) is characterised by several genetic, clinical and neuroimaging phenotypes which can be transmitted in a dominant (*SLC20A2*, *PDGFRB*, *PDGFB* and *XPR1*), recessive fashion (*MYORG* and *JAM2*). Although parkinsonism and dystonia are the most frequently observed phenomenology, there is a wide variable phenotypical expressivity. Furthermore, the different genetic subtypes of PFBC cannot be distinguished on clinical grounds alone. *SLC20A2* pathogenic variants are the most common cause of PFBC, and 13% of the cases feature parkinsonism where focal dystonia can be present in some. [99] *MYORG* pathogenic variants, with characteristic pontine calcifications, can feature focal dystonia in some cases.[100] Recently, disorders in calcium metabolism due to *ALPL* [101] and *CaSR* pathogenic variants [102] have been associated with dystonia-parkinsonism as the presenting phenotype.

Neurometabolic disorders such as Niemann-Pick type C and cerebrotendinous xanthomatosis may feature atypical parkinsonism and dystonia as part of their phenotypic spectrum, and in some cases, could be the presenting feature.[103] The presence of characteristic features of each of these disorders is helpful to suggest their diagnosis. The association of non-neuronopathic form of Gaucher's disease due to recessive GBA1 pathogenic variants and parkinsonism is well established, and presentations with atypical parkinsonism and cognitive features may include axial or limb dystonia.[104] Rarely, spinocerebellar ataxias can initially present with a dystonia-parkinsonism phenotype, especially SCA3, SCA17 and SCA12 [105]. Nevertheless, patients with a cerebellar presentation

due to SCA1-2 [105] SCA8 [105], SCA14 [106] and SCA48 [107] may also feature dystonia and parkinsonism. In patients with leukodystrophy and adult-onset parkinsonism, autosomal dominant *CSF1R* pathogenic variants should be considered [108].

Dystonia-parkinsonism in late adulthood (50-80 years)

Dystonia-parkinsonism starting >50 years is commonly associated with neurodegenerative disorders, such as Parkinson's disease and multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBS). The distribution and pattern of dystonia in these disorders have been well delineated in recent reviews. **[109]** Briefly, orofacial dystonia, antecollis and truncal dystonia are common in MSA-parkinsonian subtype, whereas blepharospasm, facial and retrocollis are indicative of PSP. A peculiar dystonia posture, "pointing gun posture" (extension of index finger and thumb) has been described in up to 26% of patients with PSP.[110] Unilateral or asymmetrical arm dystonia is characteristic in patients CBS, where spreading to the ipsilateral lower limb occurs with progression.

Pathogenic variants in *LRRK2*, *SNCA* and *VPS35* present as Parkinson's disease with variable presence of dystonia, usually in a focal distribution. In a systematic review of *SNCA* phenotypes, atypical signs were seen in 83% of cases, but dystonia was reported only in 8% of cases [111]. In *LRRK2*, dystonia was reported in 38%, and in *VPS35* in 3%.

Genetic neurodegenerative dementias can present as a predominant movement disorder, mainly parkinsonism. A systematic review of genetically proven frontotemporal dementias (FTLD) and a recent neuropathological study highlighted that approximately a third of patients had an initial presentation of movement disorders, most frequently parkinsonism with dementia or CBS and PSP. [112, 113] *C9ORF72* expansions most commonly manifest parkinsonism and tremor as their main movement disorders, but presentation with cervical and hand dystonia in cognitively affected patients has been reported. Clinical descriptions of dystonia in *C9ORF72* suggests that the neck may be the most frequently affected region, but hemidystonia and upper limb dystonia can be seen.[114, 115] Predominant dystonia-parkinsonism has not been reported as the initial presentation. Rarely, sporadic [116] and genetic Creutzfeldt-Jakob disease with *PRNP* P102L pathogenic variants [117] and with genetic

Alzheimer disease due to *PSEN1* pathogenic variants [118] can present as dystonia-parkinsonism often on a background of progressive cognitive decline.

Complex phenotypes with ataxia, parkinsonism and cervical dystonia or parkinsonism with focal dystonia have rarely reported in patients with *SPG7*, where pyramidal signs may be variably present. [119, 120] One case with pyramidal signs, ataxia, dystonia and parkinsonism has been reported in a patient with *SPG76* [121]. Mitochondrial disorders in adulthood (*POLG* pathogenic variants) can also feature dystonia-parkinsonism; however, these usually have suggestive features such as ophthalmoparesis, sensory axonal neuropathy and basal ganglia lesions.[122]

Conclusions and future perspective

Dystonia-parkinsonism is a syndrome with a myriad of aetiologies, some of which with specific treatment implication that shouldn´t be missed. Many of the acquired causes of dystonia-parkinsonism can be recognized by phenomenology (e.g. tardive syndrome) or by neuroimaging (structural lesions). Likewise, infectious and autoimmune aetiologies are diagnosed through targeted CSF analysis and autoantibody testing respectively. Genetic dystonia-parkinsonism has a wide and broadening differential diagnosis, and disorders that commonly present with dystonia-parkinsonism should be considered first. The differential diagnosis depends primarily on the combination of age at onset, associated clinical features, the tempo of disease progression, and the response to L-dopa. Brain MRI and in some cases, DAT scan, are very useful investigational tools to tailor subsequent diagnostic approaches.

From a pathophysiological viewpoint, the coexistence of commonalities and differences between dystonia and parkinsonism remain intriguing.

Some recent studies suggest further links and overlaps: in patients with *KM2TB* [132, 133] and *ANO3* [134] pathogenic variants, typically causing monogenic dystonia, parkinsonism has been observed. In the literature, cases of initial focal hand, cranial or cervical isolated dystonia with latter emergence of parkinsonism (even after decades) have been reported.[135, 136] These observations require confirmation by others and further research, to better understand possible associations and pathophysiological links.

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