Secondary dystonia – clinical clues and syndromic associations

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Dystonic syndromes can be divided into primary and secondary forms. Diagnosis of secondary dystonic syndromes can be challenging as causes are multifold. They include brain lesions of various origins, metabolic disease, neurodegenerative conditions, or following exposure to drugs or toxins. However, characteristic investigational findings may be directive in the diagnostic process and facilitate making the correct diagnosis and thus allow initiating the ideal treatment. In this article, we point out some clinical clues and syndromic associations which may be helpful in the approach to a patient with dystonia.

Dystonia is defined by involuntary sustained muscle spasms resulting in twisting movements and abnormal posturing of one or more body parts. Etiologically, dystonic syndromes can be broadly divided into primary and secondary forms, dystonia-plus syndromes and heredodegenerative forms. In recent years, numerous authors have reviewed the primary dystonias [1].

In this article, we chose to focus on secondary and complex dystonia syndromes particularly, because their diagnosis can be challenging as causes are multifold. They include brain lesions of various origins, metabolic disease, neurodegenerative conditions, or following exposure to drugs or toxins. However, characteristic clinical clues and investigational findings may be directive in the diagnostic process and facilitate making the correct diagnosis and thus allow initiating the ideal treatment. In this article, we point out clinical clues (Fig. 1 and Table 1) and syndromic associations (Table 2) which may be helpful in the approach to a patient with dystonia.

Prevalence data on secondary dystonia are limited. In a Brazilian cohort of 122 patients with a dystonic syndrome, 46 (38%) had symptomatic dystonia [2]. Amongst these, tardive dystonia was the most frequent cause (35%) followed by perinatal cerebral injury (30%). Other causes included stroke (13%), encephalitis (6.5%), and Wilson’s disease (4%). Cranial trauma, mitochondrial cytopathy, and psychogenic were the least frequent causes with one patient each. In two patients, the etiology could not be established. Perinatal cerebral injury and post-encephalitic dystonia were seen in the younger age group, whilst post-stroke and tardive dystonia were seen in the older age group. In a recent study, Wenning et al. [3] examined a total of 706 men and women aged 50–89, 16 of which were found to have dystonia. Amongst these, ten patients (62.5%) were classified as secondary dystonia, of which eight were drug-induced, whereas in the remaining two a diagnosis of edentulous dystonia was suspected. Similarly, a big study of more than 3000 patients with dystonia, 29% of which were thought to have a secondary form, found tardive dystonia to be the leading cause of secondary dystonias [4,5]. However, there are a number of other secondary and heredodegenerative disorders that can cause dystonia as a predominant feature or part of a syndrome. Here, we suggest clinical clues which may help narrow the differential diagnosis and help focus the investigations accordingly.

Clinical clues

Dystonia with prominent oromandibular or laryngeal involvement

Prominent oro-lingual-buccal dystonia is uncommon in primary dystonia, although in some primary dystonias there may be laryngeal involvement, for example in DYT4 (‘whispering dystonia’), DYT6 (associated with mutations in the THAP1 gene), DYT12 (rapid-onset dystonia-parkinsonism associated with ATP1A3 gene mutations), and DYT17 (linked to the chromosome 20) [6–8]. However, marked oro-bulbar involvement usually indicates a secondary or heredodegenerative form [9]. Presence of severe orobulbar involvement should alert the clinician to exclude previous neuroleptic intake, but also certain genetic disorders such as...
pantothenate kinase-associated neurodegeneration (PKAN, previously known as Hallervorden–Spatz disease) because of mutations of the PANK2 gene, neuroacanthocytosis, neuroferrinopathy, and Lesch–Nyhan syndrome [9].

**Dystonia and peripheral neuropathy**

Neuropathy is not a feature of primary dystonias. In the combination with ataxia, dystonia and peripheral neuropathy are seen in young patients with Niemann-Pick type C disease, an autosomal recessive neurovisceral lipid storage disorder, whilst peripheral nervous system involvement is not a usual feature of the adult form [10]. Because the presence of vertical gaze palsy is a characteristic feature, which is present in 75–80% of patients, this can be a helpful clue toward the diagnosis.

### Table 1 Features suggestive of secondary dystonia

| Features                                                                 | Investigation                                                                                                                                 |
|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Sudden onset and rapid progression                                       |                                                                                                                                               |
| Hemidystonia                                                            |                                                                                                                                               |
| Cranial onset in childhood                                               |                                                                                                                                               |
| Restriction to focal or segmental dystonia with childhood-onset         |                                                                                                                                               |
| Onset in legs in adults                                                  |                                                                                                                                               |
| Progression to generalized dystonia with adult-onset                    |                                                                                                                                               |
| Prominent oro-bulbar involvement                                        |                                                                                                                                               |
| Other neurological or systemic signs                                     |                                                                                                                                               |
| Presence of painful spasms (as in tonic spasms)                         |                                                                                                                                               |

### Table 2 Examples of syndromic associations. Clinical clues

| Features                                                                 | Differential diagnosis to consider                                                                                                                                                                                                 | Investigation                                                                                                                                 |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Dystonia with prominent oromandibular involvement                      | - Drug-induced (e.g. neuroleptics, antiemetics)                                                                                                      |                                                                                                                                               |
|                                                                         | - PANK2 gene, iron deposition on MRI                                                                                                                 | - PL2G6 gene                                                                                                                                 |
|                                                                         | - PLA2G6-associated neurodegeneration                                                                                                                | - Acanthocytes screen, protein assay, VPS13A gene test                                                                                     |
|                                                                         | - Neuroacanthocytosis                                                                                                                                | - FTL gene, iron deposition on MRI                                                                                                          |
|                                                                         | - Neuroferritinopathy                                                                                                                                | - Serum and urinary uric acid, HPRT1 gene                                                                                                  |
|                                                                         | - Lesch-Nyhan disease;                                                                                                                               | - Alpha-fetoprotein, in vitro radiosensitivity, ATM levels on western blotting, ATM gene                                                  |
|                                                                         | - Nieman-Pick type C                                                                                                                                   | - Genetic testing (e.g. Atx3 etc)                                                                                                           |
|                                                                         | - Metachromatic leukodystrophy                                                                                                                       |                                                                                                                                               |
|                                                                         | - Friedrich ataxia                                                                                                                                     |                                                                                                                                               |
|                                                                         | - Ataxia telangiectasia                                                                                                                                |                                                                                                                                               |
|                                                                         | - Spinocerebellar ataxias (e.g. SCA3)                                                                                                                |                                                                                                                                               |
| Dystonia and peripheral neuropathy                                       | - Nieman-Pick type C (supranuclear gaze palsy)                                                                                                      | - NPC1 and NCP2 gene                                                                                                                        |
|                                                                         | - Huntington’s disease (apraxic eye movements)                                                                                                      | - IT15 / HD gene                                                                                                                           |
|                                                                         | - Ataxia telangiectasia (apraxic eye movements)                                                                                                     | - Alpha-fetoprotein, in vitro radiosensitivity, ATM levels on western blotting, ATM gene                                                  |
| Dystonia and eye movement disorders                                      | - PKAN                                                                                                                                                |                                                                                                                                               |
|                                                                         | - GM2 ganglosidosis                                                                                                                                     |                                                                                                                                               |
| Dystonia and retinitis pigmentosa                                       | - Metachromatic leukodystrophy                                                                                                                       |                                                                                                                                               |
|                                                                         | - Mitochondrial disease                                                                                                                                |                                                                                                                                               |
|                                                                         | - Mohr-Tranebaerg syndrome                                                                                                                              |                                                                                                                                               |
|                                                                         | - Woodhouse-Sakati syndrome                                                                                                                            |                                                                                                                                               |
| Dystonia and deafness                                                   | - Dopa-responsive dystonia                                                                                                                             |                                                                                                                                               |
|                                                                         | - Young-onset Parkinsonism (e.g. Parkin)                                                                                                                | - GTP1 cyclohyrolase gene, tyrosine hydroxylase gene and other genes; CSF analysis, DAT SPECT, Dopa-challenge                              |
|                                                                         | - Wilson’s disease                                                                                                                                     | - Genetic testing (e.g. Parkin gene, etc.)                                                                                                  |
|                                                                         | - Kufor-Rakeb disease                                                                                                                                   | - Copper/caeruloplasmin, slit lamp examination, (ATP7B gene)                                                                               |
|                                                                         | - PLA2G6-associated neurodegeneration                                                                                                                 | - ATP13A2 gene                                                                                                                                 |
|                                                                         | - Atypical Parkinsonian disorders: PSP, CBD, MSA                                                                                                     | - PLA2G6 gene                                                                                                                               |
|                                                                         | - Levodopa-induced dyskinesia in PD                                                                                                                    |                                                                                                                                               |
| Dystonia with progressive dementia                                       | - GM1, GM2 ganglosidosis                                                                                                                               | - Urine oligosaccharides; Mutations in the beta-galactosidase HEX-A and HEX-B gene, enzymatic function test | - GCDH gene                                                                                                                             |
|                                                                         | - Glutaric acidemia                                                                                                                                     | - IT15 / HD gene                                                                                                                           |
|                                                                         | - Huntington’s disease                                                                                                                                  | - PRNP gene, JPH3 gene, TBP                                                                                                                  |
|                                                                         | - Huntington’s disease look-alike disorders (e.g. Prion disease, SCA17)                                                                            |                                                                                                                                               |

CBD, corticobasal degeneration; MSA, multiple system atrophy; PSP, progressive supranuclear palsy.
Enlargement of the liver and spleen (present in about 30–90% of cases) [10,11] and in children neonatal jaundice (present in half of the patients) can also be directive signs.

Mutations in the arylsulfatase A gene cause metachromatic leukodystrophy, a disorder characterized by progressive dystonia, ataxia, and cognitive decline, accompanied by peripheral neuropathy [12]. Other recessive ataxia syndromes, such as Friedreich’s ataxia [13] and ataxia telangiectasia [14,15], also come into consideration when ataxia, dystonia, and peripheral neuropathy are present. For example, in a study of 70 patients with ataxia telangiectasia, dystonia was present in 55 and peripheral neuropathy in 50 of them [14]. The combination of dystonia with neuropathy and ataxia can also be seen in some of the autosomal dominant spinocerebellar ataxias [16], e.g. SCA 3[17].

**Eye movement disorders**

In patients with primary dystonia, normal eye movements are expected. Thus, presence of an eye movement disorder may hint toward a secondary form of dystonia.

One example is the combination of supranuclear gaze palsy and dystonia. Patients with a supranuclear gaze palsy may complain of difficulty going downstairs because of limited downward gaze. The differential diagnosis includes most importantly progressive supranuclear palsy (PSP), Kufor Rakeb disease (associated with mutations in ATP13A2) and Niemann-Pick type C. In the latter condition, supranuclear gaze palsy is present in 75% of adult-onset cases and a presenting sign in 8% of cases [10]. Patients with supranuclear gaze palsy may complain of difficulties going downstairs because of limited downward gaze, which is usually more affected than upward gaze.

**Dystonia and retinitis pigmentosa**

The presence of retinitis pigmentosa in the context of dystonia narrows down the list of differential diagnoses. Most important differential diagnoses in this context are PKAN (pantothenate kinase-associated neurodegeneration or HARP syndrome characterized by hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), GM2 gangliosidosis, and metachromatic leukodystrophy.

**Dystonia and deafness**

The combination of dystonia and deafness is a characteristic feature of mitochondrial disease including the Mohr-Tranebjaerg syndrome because of mutations in

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**Figure 1** Algorithm for the classification of dystonia.

No other features

- Young-onset → generalization; Late-onset → remaining focal

- Acute onset; Rapid progression; Hemidystonia; Young-onset → remaining focal; Late-onset → generalization; Leg-onset in adults; Prominent oro-bulbar involvement

**Suggestive of**

- Primary Dystonia
- Secondary Dystonia

- Additional features: Retinitis pigmentosa, deafness, Parkinsonism, progressive dementia, seizures, eye movement disorder

- Investigational work-up normal
- Abnormal findings on investigational work-up

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the DDPI gene [18]. Other mitochondrial disorders may produce more complex phenotypes including additional visual problems (blindness) or heart problems [19]. Another complex disorder with phenotypic similarities to mitochondrial disease is the Woodhouse-Sakati syndrome that has recently been found to be because of mutations in the C2orf37 gene, encoding a nucleolar protein [20]. This rare autosomal recessive disorder presents with hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal features [21].

Dystonia and parkinsonism

On the one hand, dystonic conditions may have superimposed parkinsonism as seen in dopa-responsive dystonia or Wilson’s disease.

On the other hand, dystonia may be seen in (or even be the presenting feature of) various parkinsonian disorders. Here in yet untreated patients with parkinsonism dystonia is uncommon and may thus be a pointer toward a condition other than idiopathic Parkinson’s disease, such as atypical parkinsonian syndromes like PSP, multiple system atrophy (MSA), or corticobasal degeneration (CBD)[22]. Dystonia may then present as axial dystonia and blepharospasm (levator inhibition) causing the staring expression associated with PSP; facial dystonia and antecollis-like postures in MSA or the dystonic arm posture seen in CBD.

Parkinsonism and dystonia is also characteristic of genetic forms of parkinsonism, which often have young-onset (for example because of Parkin mutations). In Parkin-related parkinsonism, dystonia may be present intermittently, as exercise-induced paroxysmal foot dystonia, and this may even be a presenting feature [23]. The combination of young-onset dystonia and parkinsonism is also seen in other neurodegenerative diseases, including the rare autosomal recessive disorders such as the nigro-striatal-pallidal-pyramidal syndrome of Kufor-Rakeb disease or PLA2G6-associated neurodegeneration (PARK14) [24] (also see review by Schneider et al.[25]).

More frequently, however, dystonia in the context of parkinsonism is seen as a complication of dopaminergic treatment, for example as peak-dose dystonia, diphasic dystonia, and off-dystonia [22].

Dystonia with progressive dementia

Progressive dementia is one of the core features of Huntington’s disease and the Huntington disease-look like syndromes (including SCA17), as well as neuroacanthocytosis and PKAN. Although chorea is the main movement disorder, prominent dystonia, mainly focal, can occur.

Creutzfeldt-Jakob disease is a rare neurodegenerative disease characterized by rapidly progressive dementia, mutism, ataxia and extrapyramidal and pyramidal involvement [26]. Although focal or generalized myoclonus is the most common movement disorder (present in 80–100% of cases), dystonia occurs and may rarely be a presenting sign [26–28]. Dystonia in Creutzfeldt-Jakob disease is usually unilateral and distally but may become generalized in later disease stages [26]. Dementia may also be a symptom in the complex autosomal recessive dystonia parkinsonian syndromes [25].

Clues from neuroimaging

In addition to clinical clues, neuroimaging can point toward certain diagnoses. Lesions in the basal ganglia, brainstem, cerebellum, or cortical areas (parietal and frontal) may result in dystonia [29–36]. Whilst not all BG lesions necessarily result in neurological symptoms or signs, it has been suggested that there is a relationship between the distribution of dystonia and the localization of the lesion. It has been proposed that thalamic lesions are more likely to result in hand dystonia. Brainstem lesions on the other hand may be found in cranial dystonias such as blepharospasm, and putaminal lesions have been associated with hemidystonia or limb dystonia. In hemidystonia, lesions are often unilateral, contralaterally to the dystonia. The nature of the lesion may be multifold and includes tumors, trauma, bleeding, inflammation, atrophic changes in the context of neurodegeneration, or accumulation of metals (such as iron, copper, and manganese etc.). As an example of how imaging can facilitate the diagnostic work-up, we will in the following discuss aspects of basal ganglia metal deposition.

The basal ganglia host high concentrations of metals such as iron, copper, and manganese that act as cofactors for metabolic activity. However, excessive metal accumulation may cause dysfunction and disease and can be detected by neuroimaging. In recent years, in particular, iron deposition has received growing attention and the term of ‘syndromes of neurodegeneration with brain iron accumulation’ (NBIA) has been coined. This group entails the condition of PKAN, PLA2G6-associated neurodegeneration [24], Kufor Rakeb disease [37] neuroferritinopathy, and aceruloplasminemia [38,39]. In PKAN (NBIA type 1), also known as Hallervorden–Spatz disease, iron deposits are seen within the globus pallidus interna. On T2-weighted MRI, a rim of signal hypointensity (iron deposition) bears a central hyperintensity (probably representing fluid accumulation or edema). This has been described as the ‘eye-of-the-tiger’ sign [38] and is said to be highly correlated with PANK2 gene mutations [38,40] and is usually present early in the
disease course [41]. NBIA type 2, due to mutations of the PLA2G6 gene on chromosome 22q13, may present with a clinical picture indistinguishable from PKAN. However, iron deposition on MRI is not in form of the classical eye-of-the-tiger sign, but there is only a hypointensity in the globus pallidus. Normal MRI has also been reported in a gene-proven case [24].

Copper deposition (seen as hyperintensities on T2-weighted scans) in the putamen and globus pallidus, liver, and cornea are characteristic of Wilson’s disease [42,43], as is the so-called ‘face of the giant panda’ sign (referring to the combination of high signal intensity in the tegmentum except for the red nucleus with preservation of signal intensity of the lateral portion of the pars reticulata of the substantia nigra and hypointensity of the superior colliculus) [44].

Manganese accumulation in the basal ganglia, presenting as symmetrical pallidal hyperintensity on T1 sequences, can cause secondary parkinsonism and may occur in welders chronically exposed to manganese. Dystonia may also be prominent [45–48].

Calcium deposition within the basal ganglia is mostly confined to the globus pallidus. Incidental calcifications are relatively frequent (up to 1.5% of CT scans) and are easily detected as high-intense lesions on CT imaging. On MRI, calcifications appear as low-intensity signal on T2-weighted planes and as low-intense or high-intense signal on T1-weighted images [49]. Calcifications are usually benign and are most often idiopathic or age-related [49]. Cohen et al. suggested that calcifications of the globus pallidus require further elaboration only when found in patients younger than 40 years of age and in all patients where other basal ganglia or brain areas are affected. The differential diagnosis is wide. The main etiologies that have to be considered in such patients include metabolic, infectious, toxic-induced, and degenerative forms [49]. Amongst the metabolic disorders, idiopathic or surgical hypoparathyroidism is thought to be the most common cause of symmetric basal ganglia calcification, and dystonia as presenting feature may occur [50]. Infections (including congenital forms) by toxoplasmosis, rubella, cytomegalgy, herpes, and HIV may result in basal ganglia damage with calcifications and secondary dystonia [51,52]. Following carbon monoxide poisoning movement disorders including dystonia may develop as a part of delayed encephalopathy [53] and imaging may reveal basal ganglia calcifications [54]. An example of neurodegenerative causes of calcium deposition is Wilson’s disease [55]. Finally, there are also familial forms of basal ganglia calcifications (also referred to as striopallidoidentate calcinosis or Fahr’s disease) [55]. Manyam et al. [55] found that movement disorders affected half of the patients with symptomatic Fahr’s disease, of which parkinsonism was most frequent, but dystonia was also seen.

Conclusions
A thorough clinical examination may reveal signs atypical of primary dystonia. Here, syndromic associations, some of which have been discussed above, may help the clinicians to narrow down the list of differential diagnoses. In these patients, appropriate investigations including neuroimaging may help to reach a diagnosis.

Conflicts of interest
None.

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