Complicated Recessive Dystonia Parkinsonism Syndromes

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Abstract: In addition to pure PD and pure dystonic syndromes, there are a group of disorders with overlapping features. The differential diagnosis of these dystonia parkinsonism syndromes can be complex. In view of the growing list of recognized disorders and recent advances in genetics, we review the autosomal recessive forms of dystonia parkinsonism, summarizing clinical presentations, results of investigations, and response to treatment of gene-proven cases. We concentrate on PANK2-, PLA2G6-, ATP13A2-, FBX07, TAF1-, and PRKRA-associated neurodegeneration. Parkin, PINK1, and DJ-1 are also briefly reviewed. © 2009 Movement Disorder Society

Key words: dystonia; parkinsonism; genetic; recessive; NBIA

In recent years, there have been reviews on both Parkinson’s disease (PD)1–3 and dystonia4,5 as well as on the advances in genetics with respect to these disorders. However, in addition to pure PD and pure dystonic syndromes, there are a group of disorders with overlapping features, some of which have broadly intermediate and more complex phenotypes. The differential diagnosis of these dystonia parkinsonism syndromes can be complex including primary and secondary forms. Various dominantly, recessively and x-linked inherited genes underlying dystonia parkinsonism have recently been and continue to be identified. These have been enumerated as DYT1s and PARKs in a list of dystonia- and Parkinson-associated genes, respectively. In view of the growing list of recognized genetic disorders, we will review the recently identified syndromes of recessive dystonia parkinsonism. These include conditions which have been classified under PARK or DYT genes, and neurodegeneration with brain iron accumulation (NBIA) disorders. Here we will concentrate on PANK2-, PLA2G6-, ATP13A2-, FBX07, TAF1-, and PRKRA-associated neurodegeneration. PARK2, -6, and -7 are also briefly discussed. We will summarize clinical presentations, results of investigations, and response to treatment of gene-proven cases. We will discuss the clinical approach and possible differentiating features and speculate on possible shared pathophysiological mechanisms. In view of space limitations, dominant forms will not be discussed in this review.

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 1—PANTOTHENATE KINASE-ASSOCIATED NEURODEGENERATION

Pantothenate kinase-associated neurodegeneration (PKAN), also referred to as “neurodegeneration with brain iron accumulation” type 1, was first described by Hallervorden and Spatz6 in 1922 and, in 2001, was found to be due to mutations in the Pantothenate kinase 2 (PANK2) gene on chromosome 20p13 (OMIM 234200). Numerous mutations including point mutations and exon deletions have been reported.7 In addition to numerous historical reports based on clinical or pathological diagnosis, the number of genetically proven cases is now also rising.

The mean age of onset of recognized PKAN is around age of 3 to 4 years and in almost 90% of cases...
onset occurs before age 6.8,9 However, gene-proven cases with later onset (in the 20s and 30s) have also been reported9,10 and it is likely that cases with later onset are not always being recognized.

In three quarters of gene-proven cases the presenting symptoms were gait or postural difficulties.9 The phenotype is nearly always characterized by extrapyramidal symptoms, particularly generalized dystonia with often prominent oromandibular involvement,11 chorea, and parkinsonism. Pyramidal signs (spasticity, hyperreflexia, extensor toes) develop in about a quarter of patients.9 Cognitive features with behavioral changes, e.g. obsessive compulsive behavior, aggression, or depression,12 followed by dementia are seen in a third of patients. Such signs may even be the presenting symptom in late-onset atypical PKAN cases (for example palilalia).9 In these patients with later onset (atypical cases) extrapyramidal features may also be less severe.

Analysis of gene-proven cases also revealed presence of retinopathy as demonstrated by electroneuroretinography in almost three quarters of cases with classic early-onset PKAN; but this too was less common in those with later onset.9

Pathologically, there is brown discoloration of the globus pallidus and substantia nigra with iron deposition most abundantly in the globus pallidus interna.6 The pallidal abnormalities can also be demonstrated in vivo by neuroimaging. The iron deposits (shown as pallidal hypointensity) are best detected using T2*-weighted MRI. The combination of such hypointensity with a central hyperintensity (probably representing fluid accumulation or edema) is referred to as ‘eye of the tiger’ sign.13

For NBIA-1 it is this ‘eye of the tiger’ sign which appears highly correlated with the genetic status and the presence of PANK2 mutations.9,14 However this is still debated.15 On the other hand, patients with other NBIA syndromes (without PANK2 mutations but mutations in other genes, for example PLA2G6-related NBIA, see below) do not show the typical ‘eye of the tiger’ sign. Here, there is iron deposition only without central hyperintensity.14

Concentration of striatal dopamine reuptake transporters as measured by dopamine transporter (DAT) SPECT scan is generally normal in patients with PKAN,16,17 although abnormal results have also been reported (in a gene-proven late-onset case with personality changes, choreoathetosis, and tremor who had however been treated with long-term neuroleptics).10

More recently, the role of PANK2 mutations and polymorphisms in idiopathic PD has been assessed; no mutations were found in 339 patients with typical features and late-onset.18

NEURODEGENERATION WITH BRAIN IRON ACCUMULATION TYPE 2 ASSOCIATED WITH PLA2G6 GENE MUTATIONS/PARK 14

Not all patients with iron deposition in the basal ganglia of course are positive for PANK2 mutations. Some of the remaining patients with iron deposition and a phenotype of dystonia parkinsonism and recessive inheritance may bear mutations in the PLA2G6 gene on chromosome 22.19 Mutations in this gene have been associated with infantile neuroaxonal dystrophy (INAD)19 and because some of these children have iron deposition, this was classified as NBIA-2.

Pathologically, PLA2G6- and PANK2-associated neurodegeneration are classified as neuroaxonal dystrophies. These disorders are characterized by distended axons (“spheroid bodies” or “Axonschollen”) which are widely distributed throughout the CNS, neuron loss, and astrocytic proliferation. While neuropathological findings in PKAN are abundant mainly in the globus pallidus, substantia nigra, and nuclei of the posterior columns, changes are more widely distributed in PLA2G6 gene mutation positive cases.20

Clinically, PLA2G6-encoded INAD (OMIM 256600) is characterized by early-onset progressive motor and mental retardation, cerebellar ataxia, marked truncal hypotonia, pyramidal signs, and early visual disturbances.21 Diagnostic criteria for classic INAD as established at the First Scientific Meeting on INAD are given in Table 1. Onset is in infancy and death occurs within a few years. For instance, in six PLA2G6 gene-proven INAD cases, onset was between 10 and 18 months and death occurred at age of 7 to 10 years.22 In these cases with a molecularly confirmed diagnosis, progressive cerebellar atrophy was the earliest sign on MRI. Soon, patients developed the hypointensity of the globi pallida (suggesting iron accumulation), noted on T2, T2*, and proton density weighted images. The iron was seen in the medial and lateral portions of the pallidum. However, the signal abnormality differed from the “eye of the tiger” sign of PKAN in that there was no central hyperintensity.

Recently, we reported adult-onset cases of gene-proven PLA2G6-related neurodegeneration without brain iron on MRI.26 Patients from two unrelated families of Indian/Pakistani descent presented with subacute onset of dystonia-parkinsonism, pyramidal signs, eye movement abnormalities, cognitive decline, and psychiatric features with onset age of 10 to 26 years. Cerebellar
features which are typically present early in the disease course of the early-onset variant of \textit{PLA2G6}-related neurodegeneration were absent. Notably, brain imaging revealed absence of iron deposition on brain imaging (using T2*-weighted, iron-sensitive MRI) and MRI was completely normal in the one of the patients. Another patient had some cortical atrophy and white matter changes. Patients all responded well to dopaminergic treatment; however, early development of levodopa-induced dyskinesias was reported. In view of the prominent parkinsonian features, the gene has been allocated the PARK 14 locus (however, there is no OMIM number for PARK14 yet).

In addition to these classic infantile forms, “atyypical” cases\textsuperscript{23} and “juvenile” forms\textsuperscript{24,25} of neuroaxonal degeneration have also been described in the literature. However, these date back to the era before genetic analysis and it remains unclear whether these are due to mutations in this gene.

In time it is possible that a yet broader phenotype of \textit{PLA2G6} mutation carriers will emerge. For example, the impact of \textit{PLA2G6} on schizophrenia has recently been investigated; however, results were controversial.\textsuperscript{27,28} \textit{PLA2G6} encodes a Group IV calcium-independent A2 phospholipase which plays a role in catalyzation of fatty acid release from phospholipids. It has been suggested that because of the clinical and pathological similarity of PKAN- and \textit{PLA2G6}-related neurodegeneration the associated gene products may lie on a single biochemical pathway and that other genes involved in remaining similar syndromes may map to this same, as yet uncharacterized pathway.\textsuperscript{26}

### FBXO7

Recently, a complicated pyramidal extrapyramidal syndrome associated with \textit{FBXO7} gene mutations has been described in one family. Onset was in childhood with dystonia. Some family members developed additional levodopa-responsive parkinsonism with bradykinesia and rigidity but no tremor. Onset of lower limb pyramidal signs was in the third decade. Cerbellar features and dementia were absent. Investigations including MRI were normal. Little is yet known about this syndrome.

### PARK 2—PARKIN

Parkin-related parkinsonism (OMIM 602544) is a common cause of autosomal recessive “young-onset PD”. It accounts for approximately half of the familial cases with disease onset before age 40 and for 75\% in those with onset age 20 years or younger (juvenile PD). On the other hand, parkin mutations are unlikely (<5\%) in patients with later onset (after age 30 years).\textsuperscript{29} The clinical phenotype is dominated by levodopa-responsive parkinsonism with a benign course and a correlation between onset age and evolution.\textsuperscript{30–32} Dystonia usually affects the lower limbs and was a presenting sign in 40\%.\textsuperscript{29} Exercise-induced dyskinesia/dystonia as presenting sign of parkin-related parkinsonism has also been described.\textsuperscript{33} Pyramidal features in the form of brisk reflexes occur in about half of the patients.\textsuperscript{34} However, both dystonia at onset and brisk reflexes may not be a
consequence of the presence of the parkin mutation, but correlate better with the early onset age.32

Overall, no clear clinical signs distinguishing idiopathic PD from parkin-related parkinsonism have been identified, although one study suggested that sense of smell may be preserved in parkin.35 Cardiovascular-autonomic features were found absent in parkin.36 However, neuropathologically, parkin is distinct from idiopathic PD where Lewy bodies are a hallmark feature. In parkin, Lewy bodies are absent or scarce,37–39 although this remains matter of debate.40,41

Parkin mutations affect all exons, and include point mutations, small insertions/deletions and much larger deletions, and exon duplications and triplications.42 Most parkin43 patients carry two different mutations (compound heterozygotes). A genotype–phenotype analysis of 146 patients with and 250 patients without parkin mutations, suggested disease severity (as measured by the United Parkinson’s Disease Rating Scale motor score) may be greater in carriers of at least one missense mutation compared with those carrying two truncating mutations.32 The localization of the mutations also played a role; missense mutations in functional domains of parkin resulted in earlier onset.32

The role of a single parkin mutation remains controversial and it is being debated whether asymptomatic parkin heterozygotes (carriers) are predisposed to developing (late-onset) parkinsonism. Cohort studies revealed unequivocal results.44–46 However, it has been shown that carriers can have mild extrapyramidal signs and perhaps a susceptibility to behavioral disorder as well as nigrostriatal dysfunction on functional imaging,47,48 discrete abnormalities on voxel-based morphometry,49 and abnormal electrophysiological responses to transcranial magnetic stimulation.50–52

**PARK 6—PTEN-INDUCED PUTATIVE KINASE 1**

This form of autosomal recessive parkinsonism was first mapped in a Sicilian family presenting with a typical parkinsonian phenotype including slow progression of the disease, sustained response to L-dopa, and occurrence of L-dopa-associated dyskinesias of variable severity.53 Age of onset was 32 to 48 years in the index family.

Foot dystonia at onset, hyperreflexia, sleep benefit, urinary urgency, and orthostatic hypotension, cognitive and psychiatric symptoms are also common. The encoded protein is thought to play a role in oxidative stress responses.75

**PARK 7—DJ-1**

Based on the small number reported to date,75,76 it appears that the phenotype of DJ-1-associated parkinsonism (OMIM 602533, chromosome 1p) is again similar to parkin, with young onset age, slow progression, response to L-dopa. Focal dystonia and psychiatric symptoms are also common. The encoded protein is thought to play a role in oxidative stress responses.75

**PARK 9—KUFOR-RAKEB DISEASE**

Kufor-Rakeb disease (OMIM 606693) is a rare autosomal recessive neurodegenerative disease originally described in a consanguineous Jordanian family77 from the village Kufor-Rakeb, hence the name. The clinical features comprise akinetic-rigid parkinsonism with supranuclear gaze palsy as well as oculogyric dystonic spasms, facial-facial-finger mini-myoclonus, and spasticity in some. Cognitive features include dementia and visual hallucinations. Disease onset is between the ages of 12 and 15 years.77–80 A good response to L-dopa has been noted77 however L-dopa-induced choreiform dyskinesias may develop.78,80 Brain CT and MRI reveal diffuse moderate cerebral and cerebellar atrophy without abnormal basal ganglia signal, although changes may not be present in all affected individuals.78,80

Kufor-Rakeb disease is due to mutations in the ATP13A2 gene on chromosome 1p. The 26 kb-spanning gene contains 29 coding exons and encodes a
lysosomal 5 P-type ATPase. In the original family, a homozygous 22-bp duplication, leading to a frameshift and stop codon after 236 amino acids was found. Compound heterozygosity may cause a milder phenotype with early-onset L-dopa-responsive parkinsonism (Thr12Met and Gly533Arg). In this case, onset was later (age of 30 and 40 years) and there was absence of atypical features and normal brain MRI compared with the homozygous cases.

**DYT16**

Recently, the stress-response gene encoding the protein kinase interferon-inducible double-stranded RNA-dependent activator (prkra), has been identified as a cause of recessive dystonia in Brazilian families. Disease onset was between age 2 to 18 years with focal dystonia causing walking difficulties or impaired writing. Within a few years facial, cervical, and laryngeal dystonia, dysarthria, a sardonic smile, swallowing difficulties, as well as psychiatric features developed. Most of the original patients also had pyramidal signs (brisk reflexes, ankle clonus). There was bradykinesia in some. Cerebellar or sensory deficits were absent. Brain imaging was unremarkable. Patients failed to respond to anticholinergics or dopaminergic treatment.

The new locus, DYT16, thus shows phenotypic similarities to DYT12; however, onset of the latter is more abrupt and inheritance is autosomal dominant.

*PRKRA* is located on chromosome 2q31.3 and is thought to play a role as mediator of the effects of interferon and in stress response, but still little is known.

**DYT3—X-LINKED DYSTONIA-PARKINSONISM/ LUBAG DISEASE**

This form of dystonia-parkinsonism accounts for the unusually high prevalence of torsion dystonia in Panay, one of the Philippine islands. A founder mutation, some 50 meiotic generations ago (1,000–2,000 years ago) is thought to be causative for this geographical clustering.

Clinically, almost all patients present with dystonia, most commonly affecting the craniocervical region as blepharospasm, torticollis, oromandibular, lingual, and pharyngeal dystonia but also dystonia of the distal limbs. The name “Lubag disease” refers to the “twisting” nature of the disease in the local dialect. Action or resting tremor of a limb may also be an early sign. Progression to multifocal or generalized dystonia typically occurs within 5 years in most patients. In addition to the main clinical features of dystonia parkinsonism, the phenotype may include myoclonus, chorea, and myorhythmia, as shown in cases genetically confirmed by linkage analysis.

Mean age of onset is around age 30 (range, teens to 50s). All 28 cases of an early series were male and inheritance was compatible with an X-linked recessive trait. However, females may also be mildly affected.

In early disease stages, brain MRI shows minimal atrophy of the caudate and putamen or subtle putaminal signal abnormality. In later stages, when parkinsonism becomes a dominating feature, severe atrophy of the caudate and putamen as well as marked increase in signal abnormality with an outer rim of high signal in the putamen are seen.

Treatment is difficult as anticholinergics, antiparkinsonian, and antipsychotic drugs may not produce consistent beneficial effects. However, good L-dopa response was reported in a patient with prominent parkinsonian features. Botulin toxin may provide temporary relief of focal dystonia. Data on surgical experience and long-term outcome of surgery remain limited. Recently a case with a good response to bilateral pallidal stimulation has been published. However, reports have suggested that patients may have a high risk of death in early phases following surgery usually due to aspiration pneumonia.

Neuropathological studies in Lubag patients revealed neuronal loss and a multifocal mosaic pattern of astrocytosis restricted to the caudate and lateral putamen.

Recent studies suggest that reduced neuron-specific expression of the *TATA box-binding protein-associated factor 1* (*TAF1*) gene on chromosome Xq13 may play a role. The authors found a short interspersed nuclear element retrotransposon insertion in an intron in this gene and decreased expression levels of *TAF1* and the dopamine receptor D2 gene in the caudate nucleus.

**OTHER CONDITIONS TO CONSIDER**

In addition to the before-mentioned conditions, there are further PARK and DYT loci and other genes which may come into consideration for the differential diagnosis of recessive dystonia-parkinsonism, including dopa-responsive dystonia due to *tyrosine hydroxylase* mutations and Wilson’s disease. However, in these and in parkin, PINK1 and DJ-1 pyramidal signs are only mild and not as marked as in the other syndromes reviewed earlier.
<table>
<thead>
<tr>
<th>Classification/locus</th>
<th>Synonyms</th>
<th>Chromosomal location</th>
<th>Gene/protein</th>
<th>Inheritance</th>
<th>Onset age (in yr)</th>
<th>Dyst Park</th>
<th>Levodopa-resp</th>
<th>Pyr</th>
<th>Cerebell</th>
<th>Cogn/psych</th>
<th>MRI</th>
<th>DaT scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBIA 1</td>
<td>Previously: Hallervorden-Spatz syndrome; PKAN</td>
<td>20p13</td>
<td>PANK2</td>
<td>AR</td>
<td>3–6; later in atypical cases (twenties)</td>
<td>++</td>
<td>++</td>
<td>(--)</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>“Eye of the tiger” sign</td>
</tr>
<tr>
<td>NBIA 2/ PARK 14</td>
<td>Infantile neuroaxonal dystrophy (INAD), Seitelberger disease; Karak syndrome; PLA2G6-related neurodegeneration (PLAN)</td>
<td>22q12-13</td>
<td>PLA2G6</td>
<td>AR</td>
<td>(1) 1–2; (2) Early adulthood</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>$</td>
<td>++</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>PARK9</td>
<td>Kufor-Rakeb syndrome</td>
<td>1p36</td>
<td>ATP13A2</td>
<td>AR</td>
<td>12–15 # (+)</td>
<td>+</td>
<td>++</td>
<td>$</td>
<td>--</td>
<td>--</td>
<td>+</td>
<td>Cerebral and cerebellar atrophy; BG normal</td>
</tr>
<tr>
<td>---</td>
<td>FBXO7-associated Parkinsonian-pyramidal syndrome</td>
<td>22q12-q13</td>
<td>F-Box only protein 7</td>
<td>AR</td>
<td>childhood</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>Normal</td>
</tr>
<tr>
<td>DYT16</td>
<td>Lubag disease, x-linked dystonia-parkinsonism</td>
<td>2q31</td>
<td>PRKRA</td>
<td>AR</td>
<td>2–18</td>
<td>++</td>
<td>+</td>
<td>--</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>Normal</td>
</tr>
<tr>
<td>DYT3</td>
<td>--- Wilson’s disease</td>
<td>Xq13</td>
<td>TAF1</td>
<td>x-linked</td>
<td>20–50</td>
<td>++</td>
<td>+</td>
<td>(+)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>PARK2</td>
<td>Parkin</td>
<td>6q25.2-q27</td>
<td>Parkin</td>
<td>AR</td>
<td>&lt;30</td>
<td>(+)</td>
<td>++</td>
<td>++</td>
<td>(+)</td>
<td>--</td>
<td>(--)</td>
<td>Normal</td>
</tr>
<tr>
<td>PARK6</td>
<td>PINK1</td>
<td>1p36</td>
<td>PINK1</td>
<td>AR</td>
<td>30–50</td>
<td>(+)</td>
<td>++</td>
<td>++</td>
<td>(+)</td>
<td>--</td>
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<td>DJ1</td>
<td>1p36</td>
<td>DJ1</td>
<td>AR</td>
<td>&lt;40</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>--</td>
<td>--</td>
<td>(--)</td>
<td>Normal</td>
</tr>
<tr>
<td>DYT5</td>
<td>--- DRD</td>
<td>11p15.5</td>
<td>TH</td>
<td>AR</td>
<td>childhood</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>(+)</td>
<td>--</td>
<td>(--)</td>
<td>Normal</td>
</tr>
<tr>
<td>---</td>
<td>--- Wilson’s disease</td>
<td>13q14.3-q21.1</td>
<td>ATP7B</td>
<td>AR</td>
<td>teens</td>
<td>++</td>
<td>++</td>
<td>variable</td>
<td>(+)</td>
<td>--</td>
<td>High signal lesions on T1 and T2, putamina +/- other brain areas. “Panda sign” (high signal intensity in the tegmentum except 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)</td>
<td>Reduced uptake or normal</td>
</tr>
<tr>
<td>---</td>
<td>--- Rett’s syndrome</td>
<td>Xq28</td>
<td>MECP2</td>
<td>x-linked</td>
<td>childhood</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Normal in young patients; later generalized atrophy (cerebral, cerebellar, caudate)</td>
</tr>
<tr>
<td>---</td>
<td>--- GM1 gangliosidosis type 3</td>
<td>3p21</td>
<td>GLB1</td>
<td>AR</td>
<td>Mostly childhood</td>
<td>+</td>
<td>+</td>
<td>(--)</td>
<td>+</td>
<td>(+)</td>
<td>High signal lesions on T1 and T2, putamina +/- other brain areas. “Panda sign” (high signal intensity in the tegmentum except 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)</td>
<td>Reduced uptake or normal</td>
</tr>
</tbody>
</table>

Dyst, dystonia; Park, parkinsonism; Levodopa-resp, beneficial response to levodopa; Pyr, pyramidal features; Cerebell, cerebellar signs; Cogn/psych, cognitive decline or psychiatric features; PRKRA, protein kinase interferon-inducible double-stranded RNA-dependent activator; BG, basal ganglia; n.k., not known; +, present; --, absent; $, early levodopa-induced dyskinesias; #, late-onset heterozygous cases presenting as young-onset Parkinson’s disease have been described.
DISCUSSION

As outlined earlier, various genes have been identified which may cause recessive dystonia-parkinsonism. Although the number of genetically proven reported cases is still limited and there is indeed overlap between the syndromes, there may be certain clinical pointers which may help to approach these.

For example, the degree of parkinsonism compared with the severity of dystonia appears to be slightly different between these syndromes. While dystonia is predominant in PKAN, DYT16, and DYT3 (Lubag disease), parkinsonism predominates in Kufor-Rakeb disease and in genetic forms of young-onset Parkinson’s disease, e.g. parkinsonism related to Parkin, PINK1, or DJ-1 mutations, although focal dystonia may be a presenting sign. The initial distribution and the axis of spreading of dystonia also differ between the syndromes. In dopa-responsive dystonias and young-onset Parkinson’s disease, similar to DYT1-related dystonia, onset of dystonia is typically in the lower limb. In contrast, dystonia is prominent in the cranio cervical region in DYT16 and Lubag disease, and has prominent oromandibular involvement in PKAN. Presence of cerebellar signs early in the disease course may point toward PLA2G6-related INAD. Features are also summarized in Table 2.

In addition to the DYT- and PARK-designated loci, dystonia and parkinsonism may also be present in patients with Rett’s syndrome (OMIM 312750) due to a mutation in the MECP2 gene on chromosome Xq28.94,95 However, the presence of stereotyped movements often involving hands or the mouth may be a red flag for this condition.96 Finally, GM1-gangliosidosis type III (OMIM 230650) due to mutations in the GLB1 gene on chromosome 3p21 should be considered as a cause of early-onset dystonia parkinsonism, particularly in patients with a short stature and skeletal dysplasia.95,97,98 Choreoathetoid movements of the limbs and face and myoclonic jerks may be superimposed here.

MRI imaging may disclose hallmark features of basal ganglia iron deposition in the form of an “eye of the tiger” sign in PKAN. White matter lesions, cerebellar, or cortical atrophy may hint toward PLA2G6-related neurodegeneration. A “panda sign” has been described for Wilson’s disease.99 Patients with GM1-gangliosidosis type III may show hypersignal of the putamen on T2-weighted MRI.97 MRI is generally normal in Lubag disease, DYT16, and young-onset Parkinson’s disease. Similarly, a DAT scan may be helpful in the process of making a diagnosis. For example, it is normal in dopa-responsive dystonias and PKAN whereas reduced uptake is seen in the other conditions discussed earlier (Table 2).

As we have noted, the clinical and genetic classifications of these disorders obscure, rather than enlighten, the overlapping phenotypes of the syndromes we discuss. The question of whether a disorder gets a PARK or a DYT, or an NBIA label more reflects the history of research into the disorder than it does the clinical features of the diseases or their underlying genes. These disorders all can present with similar features, but often these features can be quite variable, even with the same gene mutation. While we only have symptomatic treatment, recognizing what symptoms can be treated is the most important goal. As we move to mechanistic therapies, we will need to be able to distinguish the syndromes. For accurate genetic counseling, this is already required. We hope this survey of the complex parkinsonism-dystonias is a useful guide to this complex area.

In summary, although there is overlap between the recently genetically identified disorders of autosomal recessive dystonia-parkinsonism, there are some clinical features which can be helpful to guide genetic testing to confirm a molecular diagnosis. The purpose of the review is to familiarize clinicians with the phenotypes of these disorders.

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