

Review

A Practical Approach to Early-Onset Parkinsonism

Giulietta M. Riboldi^{a,*}, Emanuele Frattini^{b,c}, Edoardo Monfrini^{b,c},
Steven J. Frucht^a and Alessio Di Fonzo^b

^a*The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Health, New York, NY, USA*

^b*IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy*

^c*Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*

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Abstract. Early-onset parkinsonism (EO parkinsonism), defined as subjects with disease onset before the age of 40 or 50 years, can be the main clinical presentation of a variety of conditions that are important to differentiate. Although rarer than classical late-onset Parkinson's disease (PD) and not infrequently overlapping with forms of juvenile onset PD, a correct diagnosis of the specific cause of EO parkinsonism is critical for offering appropriate counseling to patients, for family and work planning, and to select the most appropriate symptomatic or etiopathogenic treatments. Clinical features, radiological and laboratory findings are crucial for guiding the differential diagnosis. Here we summarize the most important conditions associated with primary and secondary EO parkinsonism. We also proposed a practical approach based on the current literature and expert opinion to help movement disorders specialists and neurologists navigate this complex and challenging landscape.

Keywords: Parkinsonian disorders, Parkinson's disease, autosomal recessive early-onset, secondary Parkinson's disease, dopa-responsive dystonia, adult-onset dystonia-parkinsonism, genetic counseling

INTRODUCTION

The term “early-onset Parkinson's disease” (EO PD, or young-onset PD - YOPD) refers to cases of PD with onset between the age of 21 and 40 years, as reported by Quinn et al. in their seminal paper from 1987, or between 21 and 50 years, according to other authors [1–4]. Compared with idiopathic cases of PD (iPD), patients with EOPD usually present a slower progression of the motor symptoms,

a prevalence of bradykinesia over tremor, focal dystonia at onset or during off-state, satisfactory response even to low doses of levodopa, earlier motor complications (such as motor fluctuations and dyskinesias), a lower incidence of cognitive impairment and non-motor symptoms, while anxiety and depression are frequent [1, 5–16]. A positive family history can be often identified in these patients, suggesting an important role of genetics in the pathogenesis of several of these cases [15, 16].

Based on retrospective observational studies, classical EOPD accounts for about 3–7% of all cases of PD in the Western world and up to 10–14% in Japan [1, 3, 17–19], with an incidence between 0.29 and 3.3 per 100,000 persons-years in the current literature [8, 17, 20, 21].

*Correspondence to: Giulietta M. Riboldi, The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU Langone Medical Center, 222 East 41st Street, 13th Floor, New York, NY 10017, USA. Tel.: +1 212 263 4838; Fax: +1 212 263 4837; E-mail: giulietta.riboldi@nyulangone.org.

In patients with EO parkinsonism, parkinsonian features can present as part of more complicated syndromes, with associated additional neurological manifestations (dystonia, pyramidal signs, cognitive impairment), psychiatric manifestations, systemic symptoms, alterations on brain imaging, and age of onset between 21 and 40 or 50 years.

Although rare, cases of EOPD or EO parkinsonism demand prompt diagnosis, as some forms can respond to treatments (i.e., PRKN-associated PD) and early interventions can prevent severe complications (i.e., Wilson's disease or ataxia telangiectasia). Primary forms of EO parkinsonism are more frequent than secondary cases due, among the others, to drug exposures or vascular accidents [22]. A significant proportion of primary forms of EO parkinsonism are due to genetic causes. Given the impressive advancements in gene-based therapeutic approaches, some patients may qualify for these treatments in the near future [23].

Because of the broad range of the differential diagnosis, significant diagnostic delays are frequent with important implications for genetic counseling for these patients and their families.

In this review, we summarized the most important genetic and systemic causes of EOPD and EO parkinsonism (Table 1, Fig. 1). We also provide a practical approach for the clinical evaluation, examination, and genetic counseling of these patients to help guide the diagnostic process and the referral to appropriate available or future treatments.

Although some of these forms can sometimes manifest before the age of 20 year, thus falling into the juvenile-onset PD (JOPD) category, here we will focus on the presentation of these various forms in the age range of 21 to 50 years.

The various etiologies of EO parkinsonism underlie distinct pathogenic mechanisms, particularly related to the genetic mutations. In general, earlier onset parkinsonism, whether in genetic or idiopathic cases, has been found to be associated with a more prominent degeneration of the basal ganglia, in certain cases lacking the classical Lewy bodies (such as in cases of PRKN-PD), with different biomarkers profiles (such as levels of p-Tau and t-Tau in the cerebrospinal fluid), molecular signatures, or with characteristic features (such as deposition of metals in the brain) due to the causative genetic mutations [24–27]. Although very interesting and certainly informative, a detailed description of the mechanistic aspects of the different forms of EO parkinsonism goes beyond the scope of this review.

METHODS

This work represents an expert opinion on this topic supported by the current literature. A narrative review of the literature was performed through a PubMed research using to the following key words: “early onset Parkinson's disease”, “early onset parkinsonism”, “young onset Parkinson's disease”, “young onset Parkinsonism”, “neurodegeneration with brain iron accumulation”, “secondary parkinsonism”, “parkinsonism” plus “lysosomal storage disease”, “mitochondrial disease”, “metabolic diseases”, “dystonia”, “ataxia”, “spasticity”, “spastic paraplegia”, “mental retardation”, “basal ganglia calcification”, “manganese”, “infectious disease”, “vascular diseases”, “Wilson's disease”.

We focused only on the works referring to cases of EO parkinsonism. We included the more relevant and comprehensive cohort studies and reviews on the topics, as well as data from single case reports or small cohort studies for the rarer conditions.

Parkinson-predominant EO parkinsonism

Genetic forms

Autosomal recessive forms. Autosomal recessive mutations in genes associated with monogenic PD are a frequent cause of EOPD [28, 29]. Among these, mutations in Parkin (*PRKN*) (missense, nonsense, deletions, insertions, multiplications) are the most common, found in 50% of PD cases with onset before age 40 [30] and in up to 77% of patients with very young-onset parkinsonism before age 20 [31]. Disease onset spans from early childhood to after 50 years in rarer instances [32, 33], with the most common occurrence in the 3rd-4th decade and a median age at onset of 31 [33]. PTEN-induced kinase 1 (*PINK1*) mutations (point mutations and rarer large deletions) are the second most common cause of autosomal recessive PD [34], found in 4–7% of sporadic EOPD cases [35, 36], with a mean age at onset of 32 years [30]. Patients with mutations in *PRKN* or *PINK1* share a similar phenotype, characterized by slow progression with robust and sustained response to levodopa. More peculiar features include onset with dystonia and symmetrical involvement, hyperreflexia, spasticity, psychiatric symptoms, and diurnal fluctuations with sleep benefit [30, 37]. Patients with *PINK1* mutations have less pyramidal signs [30] and more commonly present with psychiatric symptoms [38, 39]. Despite young or very young-onset, disease progression is slow and the

Table 1
Demographic and radiological features of the spectrum of causes of EO parkinsonism

Condition	Age of Onset	Heritability	Imaging	Response to L-dopa	Characteristic features
Primary Early Onset Parkinsonism					
Monogenic PD					
PARK- <i>PRKN</i>	Childhood to adulthood (mean 3rd-4th decade, median age 31)	AR	Brain MRI: normal	+	Dystonia (predominantly of the lower limbs, can be present at onset), symmetrical involvement, pyramidal signs, and psychiatric manifestations, excellent and sustained response to L-dopa with early motor fluctuations, sleep benefit
PARK- <i>PINK1</i>	Childhood to adulthood (mean 32 years)	AR	Brain MRI: normal	+	Dystonia and psychiatric symptoms, excellent and sustained response to L-dopa
PARK- <i>DJI</i>	Adolescence to adulthood (3rd-4th decade, median age 27)	AR	Brain MRI: normal	+	Dystonia and psychiatric symptoms
PARK- <i>ATP13A2</i>	2nd-6th decade (mean 24)	AR	Diffuse atrophy; SWI, GRE, and T2* hypointensity of basal ganglia	-/+	Vertical supranuclear gaze palsy, slow vertical saccades, pyramidal signs, facial-faucial-finger myoclonus, cognitive decline, optic atrophy
PARK- <i>PLA2G6</i>	Childhood to adulthood (most common in the 3rd-4th decade)	AR	Cerebral and/or cerebellar atrophy; SWI, GRE, and T2* hypointensity of basal ganglia; claval hypertrophy in childhood onset	-/+	Dystonia, rapid cognitive decline, psychiatric symptoms, pyramidal signs, bulbar involvement, limb ataxia, optic atrophy
PARK- <i>FBXO7</i>	2nd-6th decade (median age 17)	AR	Mild diffuse atrophy or normal brain MRI	+	Pyramidal signs, lower limb involvement, neuropsychiatric symptoms
<i>RAB39B</i> -related parkinsonism	4th-7th decade (mean age 51)	XR	CT-hyperdensity and T2 hypointensity of the basal ganglia can be seen and correspond to calcifications	-/+	Intellectual disability
<i>PTRHD1</i> -related parkinsonism	3rd-4th decade	AR	Brain MRI: normal	+	Intellectual disability, pyramidal signs, psychiatric manifestations
PARK- <i>SYNJ1</i>	2nd-3rd decade (median age 21)	AR	Diffuse atrophy, T2 white matter hyperintensity, or normal brain MRI	+	Epilepsy with infantile onset, dystonia, cognitive decline
PARK- <i>DNAJC6</i>	1st-5th decade (median age 11)	AR	Mild diffuse atrophy or normal brain MRI	+	Epilepsy with childhood onset, pyramidal signs, rapid progression with cognitive decline
<i>VPS13C</i> -related parkinsonism	Childhood to late adulthood (median age 29)	AR	Brain MRI: normal	-/+	Pyramidal signs, early cognitive impairment, autonomic dysfunction

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Table 1
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Condition	Age of Onset	Heritability	Imaging	Response to L-dopa	Characteristic features
PARK- <i>LRRK2</i>	4th-10th decade (mean age 58–61)	AD	Brain MRI: normal	+	Levodopa-responsive PD with slow progression and low incidence of dementia and psychiatric symptoms
PARK- <i>SNCA</i>	2nd-7th decade	AD	Brain MRI: normal	–/+	Cognitive decline and psychiatric features (p.Ala53Thr, p.Ala30Pro, p.Glu46Lys, dupl/tripl), pyramidal signs (p.Gly51Asp and p.Ala53Glu), myoclonus (p.Ala53Glu, dupl/tripl), cerebellar signs (p.Ala30Pro variant)
PARK- <i>VPS35</i>	4th-7th decade (mean age 51)	AD	Brain MRI: normal	+	tremor-predominant, slow progression, rare occurrence of learning disabilities, dementia, psychosis, depression
PARK- <i>GBA</i>	4th-8th decade (mean age 56.8, median 58)	AD	Brain MRI: normal	+	higher incidence of dementia, dysautonomia, and psychiatric symptoms
Metals in the brain					
Wilson's disease (<i>ATP7B</i>)	Childhood, adolescence, or early adulthood	AR	T2 hyperintensity of putamen and other deep brain nuclei ("giant panda" and "miniature panda" signs)	–/+	Wing-beating tremor, bulbar signs, dystonia, Kayser-Fleischer ring, hepatic involvement
NBIA (<i>PANK2</i> , <i>PLA2G6</i> , <i>WDR45</i> , <i>C19ORF12</i> , <i>ATP13A2</i> , <i>CP</i> , <i>FTL</i>)	Childhood (<i>PANK2</i> , <i>C19ORF12</i>), adolescence and early adulthood (<i>PLA2G6</i> , <i>ATP13A2</i> , <i>WDR45</i>), or adulthood (<i>CP</i> , <i>FTL</i>)	AR (<i>PANK2</i> , <i>PLA2G6</i> , <i>C19ORF12</i> , <i>ATP13A2</i> , <i>CP</i>), AD (<i>FTL</i> , <i>C19ORF12</i>), XD (<i>WDR45</i>)	SWI, GRE, and T2* hypointensity of basal ganglia (eye-of-the-tiger sign in PKAN, hyperintense streak of medial medullary lamina in MPAN, T1-weighted signal hyperintensity surrounding substantia nigra in BPAN, cerebellar atrophy in PLAN)	–/+	Dystonia is predominant, developmental delay, neuropsychiatric features, visual disturbances, choreoathetosis, pyramidal signs
Fahr's disease (<i>SLC20A2</i> , <i>PDGFRB</i> , <i>PDGFB</i> , <i>XPRI</i> , <i>MYORG</i> , and secondary forms)	Adulthood	AD (except for <i>MYORG</i> → AR)	Symmetrical Hyperdense TC signal involving predominantly basal ganglia (pontine involvement → <i>MYORG</i>)	–/+	Tremor, choreo-dystonic features and neuropsychiatric features, recurrent headaches
Manganese accumulation (<i>SLC30A10</i> , <i>SLC39A14</i> , and secondary forms)	Childhood (<i>SLC39A14</i>) or Early adulthood (<i>SLC30A10</i>)	AR	T1-hyperintensity of the globus pallidus and white matter, pathognomonic sparing of the ventral pons	-	hepatic involvement and polycythemia (<i>SLC30A10</i>), dystonia, "cock-walk" gait, tremor, bulbar signs

Metabolic diseases

Mitochondrial disorders (mtDNA: tRNA(Lys), tRNA(Gln), <i>ND1</i> , <i>ND2</i> , <i>ND3</i> , <i>ND6</i> , <i>Cytb</i> ; nDNA: <i>POLG1</i> , <i>TWINKLE</i> , <i>PEO</i> , <i>OPA1</i> , multiple mtDNA deletions)	Childhood-late onset	AD, AR, matrilinear	Atrophy, white-matter lesions, calcifications, cysts	+/-	Possible associated symptoms: short stature, diabetes, ophthalmoplegia, deafness, cardiomyopathy, myoclonus, seizures, and stroke like episodes
Niemann-Pick disease type C (<i>NPC1</i> , <i>NPC2</i>)	>15 years (adult form)	AR	Brain MRI: normal (cortical and cerebellar atrophy at end-stage disease)	+/-	SNGP, hepatosplenomegaly, psychiatric manifestations
Chediak-Higashi syndrome (<i>LYST</i>)	3rd-4th decade	AR	Brain MRI: normal or cortical atrophy	++	Immunodeficiency, bleeding tendency, hemophagocytic lymphohistiocytosis, and oculocutaneous albinism. Peripheral blood smear: giant inclusions in leukocytes
Ataxia Telangiectasia (<i>ATM</i>)	2nd-3rd decade	AR	Brain MRI: cerebellar atrophy	+/-	Telangiectasia, immunodeficiency, increased risk of tumors, radiosensitivity, ataxia Parkinsonism: mostly bradykinesia (less rigidity due to cerebellar hypotonia)
Cerebrotendinous Xanthomatosis (<i>CYP27A</i>)	4th-5th decade	AR	Brain MRI: cortical and cerebellar atrophy; dentate nuclei, cerebellar peduncles, and internal capsule, SN, GP, striatum T2 WM hyperintensity Dopaminergic imaging: presynaptic damage	Possible but limited	Systemic: Diarrhea, cataract, tendon xanthomas, osteopenia Neurological: cerebellar and pyramidal signs, cognitive impairment, polyneuropathy Increased serum cholestenol
Dystonia and Parkinsonism					
PARK2 (<i>PRKN</i>) (as reported above)					
PARK- <i>GCH1</i>	Dystonia (childhood), parkinsonism 2nd-3rd decade	AD	Brain MRI: normal	Remarkable at low doses with less frequent motor complications compared to EOPD	Lower limbs dystonia, diurnal fluctuations, sleep benefit
DYT- <i>PRKRA</i>	2nd-4th decade	AR	Brain MRI: normal	Limited	Young onset dystonia with opisthotonus and sardonic smile, mild parkinsonism
DYT- <i>ATPIA3</i> (RODP)	2nd-3rd decade	AD	Brain MRI: normal	Limited	Abrupt onset, limited progression, rostrocaudal progression
DYT- <i>TAF1</i>	2nd-7th decade (earlier onset in males compared to females)	X-linked recessive	Brain MRI: cortical and putaminal atrophy in advanced stages	+/-	Males>females (Panay Island), Progressive and degenerative

(Continued)

Table 1
(Continued)

Condition	Age of Onset	Heritability	Imaging	Response to L-dopa	Characteristic features
Ataxia and Parkinsonism					
SCA1-2-3-6-7-8-10-12-17-19/ 22-21, 28	3rd-7th decade	AD	Brain MRI: cerebellar atrophy	+	Nystagmus; dysautonomia is possible (SCA1,2,3); cerebellar features and spastic paraplegia (SCA28)
FXTAS (<i>FMRI</i>)	5th-6th decade	XR	Brain MRI: splenium CC, periventricular, pons, MCP WM hyperintensities (MCP sign), cortical atrophy	+	Affects males > females; parkinsonism reported in up to 28.9% cases, bradykinesia/rigidity > tremor
PEO and OA and Parkinsonism					
<i>TWINKLE</i> , <i>POLG</i>	4th-6th decade	AD (incomplete penetrance)	Brain MRI: normal	+	Ptosis, PEO, +/- SANDO precede parkinsonism
<i>SLC25A46</i>	5th-6th decade	AR	Brain MRI: WM hyperintensities	+	Possible additional mitochondrial features (neuropathy and pes cavus, hearing loss) and non-motor symptoms
Spastic paraplegia and Parkinsonism					
<i>SPG11</i>	1st-2nd decade	AR	Brain MRI: thinning of CC	+/-	Large phenotypic variability: HSP, ALS, neuropathy, parkinsonism (5–30% cases)
<i>SPG7</i>	2nd-5th decade	AR	Brain MRI: reported cortical and cerebellar atrophy	+	Parkinsonism in up to 21% cases [25]
<i>SPG15</i>	2nd decade	AR	Brain MRI: thinning CC; sign of “the ear of the lynx”	+	Lower limbs spasticity +/- dysarthria, motor neuropathy, cognitive impairment, and retinal degeneration
Intellectual disability and Parkinsonism					
<i>WDR45</i> , <i>RAB39B</i> , <i>PTHRD1</i> (as reported above) <i>PPP2R5D</i>	2nd(-4th) decade	AD	Brain MRI: possible subcortical WM hyperintensities (FLAIR) / hydrocephalus and aqueductal stenosis (1 case)	+	Mild-moderate intellectual disability and developmental delay, development of motor fluctuations with levodopa
Secondary causes of EOPD					
Drug-induced parkinsonism	Any age	NA	Normal	+/-	Underlying symptoms for which the subjects was treated with the offending drug
Infectious diseases (HIV)	Adulthood	NA	Possible focal lesions (opportunistic infections) or basal ganglia atrophy	+/-	Risk factors, additional opportunistic conditions. Inconsistent results on the role of highly active antiretroviral therapy (HAART) in causing or treating parkinsonism in AIDS
Vascular parkinsonism	Any age	NA	Ischemic or hemorrhagic lesions or vascular malformations in strategic area / leukoaraiosis	+/-	Cardiovascular risk factors

The table summarizes the different etiologies that can manifest with EO parkinsonism. Typical age of onset, mode of heritability, response to levodopa, characteristic imaging findings and distinctive clinical features are reported. AD, autosomal dominant; ALS, amyotrophic lateral sclerosis; AR, autosomal recessive; CC, corpus callosum; GRE, gradient echo; HSP, hereditary spastic paraplegia; MCP, medium cerebellar peduncle; NBIA, neurodegeneration with brain iron accumulation; OA, optic atrophy; PEO, Progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SNGP, supranuclear gaze palsy; SWI, susceptibility weighted imaging; XD, X-linked dominant; XR, X-linked recessive; WM, white matter; +, positive response; ++, robust response; +/-, inconsistent or limited response.



Fig. 1. Clinical presentation of the different forms of EO parkinsonism. Monogenic forms of EOPD and other forms of EO parkinsonism are listed on the left. For each condition the frequency of the listed clinical features (top row) is represented by the size and the color of the corresponding dot. Symptoms are described as frequent (if expected to be found in more than 75% of cases of a specific form of EO parkinsonism), present (expected to be found in 25–75% of cases), uncommon (expected to be found in <25 of cases), or absent (never reported in the specific phenotype), based on data reported in the literature and authors’ experience. Conditions were ordered according to the frequency of parkinsonian features.

incidence of dementia and dysautonomia is low [31, 33, 40–43]. An increased risk for impulse control disorders and early motor fluctuations and dyskinesias in *PRKN* carriers has been described [44]. Mutations in *DJ1* have been found in 0.4–1% of cases of EOPD [45, 46], with a median age of onset of 27

[30]. Despite their rare occurrence, *DJ1* mutations are the third most common cause of autosomal recessive EOPD after *PRKN* and *PINK1* mutations. The clinical presentation is similar to that of patients with *PRKN* or *PINK1* mutations, however a higher risk of dementia and psychiatric symptoms (i.e., depression,

anxiety, psychosis) has been reported [33, 46]. Brain MRI of EOPD associated with mutations in *PRKN*, *PINK1*, or *DJI* is usually normal.

Patients with mutations in *FBXO7* present with juvenile parkinsonism typically associated with pyramidal tract signs, thus configuring a “pallido-pyramidal” or “parkinsonian-pyramidal” syndrome [47]. Pyramidal features, comprising spasticity and hyperreflexia predominantly in the lower extremities, Babinski sign, and equinovarus deformities, present in childhood and precede the onset of parkinsonism by 5–20 years [48]. Neuropsychiatric manifestations are often present, and slow vertical saccades have been described in ~30% of patients [47, 49, 50]. Rare cases with limb myoclonus or chorea have also been reported [51]. Response to levodopa treatment is variable and often limited by dyskinesias and psychiatric complications [52, 53]. However, disease progression is usually slow and there is a low occurrence of dementia or dysautonomia [49, 52, 53]. Mild generalized atrophy can be seen, however brain MRI is often normal [48, 52, 53].

Very rare cases of rapidly progressive parkinsonism with median age at onset of 29 have been associated with mutations in *VPS13C* [54]. The course of this form is severe and characterized by early and dramatic cognitive decline, pyramidal signs, dysautonomia, and loss of ambulatory capacity within 15 years of onset [54].

Rarer autosomal recessive forms of PD present an early onset and are associated with atypical parkinsonism and complex phenotypes, often with a more severe course and are therefore discussed in the corresponding paragraphs below.

Autosomal dominant forms. Autosomal dominant forms of PD have a wide range of age at onset, from young adulthood to late adulthood, however they represent a rare cause of PD with early onset. Mutations in the *LRRK2* gene are the most common variants found in all genetic PD cases [30]. Several missense mutations are considered pathogenic, each exhibiting a characteristic ethnic distribution. The frequency of the recurrent p.Gly2019Ser mutation ranges from 1–5% among European cases to 38–39% among North African populations and 10–28% among Ashkenazi Jews [38, 55]. Mutations at the 1441 site (p.Arg1441Gly, p.Arg1441Cys, and p.Arg1441His) are more common in Spain [56]. The p.Ile2020Thr has been reported in Japanese families [57–59], and the p.Gly2385Arg has been found in kindreds in China, Japan and Korea [60–62]. Although the onset of motor symptoms in carriers

of mutations of this gene has been described as early as 28 years, the majority of mutations have been detected in late-onset cases (mean age 58–61 years) [55, 63–68]. The penetrance of *LRRK2* mutation is largely incomplete and age-related, ranging from 14% to 90% according to various studies, and thus accounting for several apparently sporadic cases [69]. The clinical phenotype of *LRRK2*-related PD is that of typical levodopa-responsive PD with a milder disease course characterized by low occurrence of depression, hyposmia, RBD, and cognitive involvement [68, 70–74].

Mutations in *SNCA* are a highly penetrant and rare cause of PD, accounting for 0.2% of sporadic PD and 1–2% of familial PD cases [38, 75, 76]. The p.Ala53Thr, p.Gly51Asp, and p.Ala53Glu variants are associated with earlier onset PD before age 50 [33, 77, 78], whereas the p.Ala30Pro and p.Glu46Lys mutations cause a form of PD with typical onset in later adulthood [79, 80]. The p.Ala53Thr, p.Ala30Pro, and p.Glu46Lys variants yield a higher risk of cognitive decline, with behavioral changes, hallucinations, and progression to severe dementia and mutism in the later stages [81]. Atypical features can be seen in specific forms: pyramidal signs have been reported in patients with p.Gly51Asp and p.Ala53Glu [82–84], with the latter also presenting with myoclonus [85], while cerebellar signs have been described in patients with the p.Ala30Pro variant [81]. In addition to point mutations, heterozygous duplications and triplications of the *SNCA* gene have also been described in kindreds with early-onset PD [86]. *SNCA* multiplications are more common in European and Asian populations, and are linked to a more severe phenotype and a well-established gene dosage effect: triplications have been associated with an earlier onset, a more rapid progression, a higher risk of dementia and dysautonomia, and atypical signs (i.e., myoclonus) [87].

Mutations in *VPS35* have a very low frequency (<1%–1.5% in PD cohorts) [88–91] and represent a very rare cause of PD [123]. The mean age at onset is 51 years [89, 92–94]; however several cases with earlier onset in the 4th–5th decade have been described [90, 91, 95]. The phenotype associated with *VPS35* mutations overlaps that of idiopathic PD of the tremor-predominant type with slow progression and good response to levodopa [30]. Atypical features are rare, however cases presenting with learning disabilities, dementia, psychosis, depression, and muscle spasms have been reported [91, 93, 96, 97].

GBA mutations are the most frequent genetic risk factor of PD, found in 5–20% of patients with PD across different populations [98–102]. A recent study screening a large cohort of PD patients identified an enrichment in GBA variants in EOPD [102]. Different variants of this gene have variable frequency across populations [103]. For example, the N370S, 84GG, E326K, and R496H variants are more frequent among Ashkenazi Jews, while the other common variant, L444P, is mostly found in non-Ashkenazi Jewish European subjects [99]. Compared with non-GBA carriers, PD patients with GBA mutations have an earlier onset of PD (median age 58) [98, 104], are more likely to develop PD before 50 years of age [98, 105], and have a higher risk and earlier presentation of non-motor features (i.e., dementia, dysautonomia, psychiatric manifestations) compared with idiopathic PD [99, 106, 107].

Secondary EO parkinsonism

Secondary causes of parkinsonism should be considered as well when assessing patients with EOPD, as they may represent treatable conditions, different from the majority of the degenerative processes. Drug-induced parkinsonism (secondary to the use of dopamine blocking agents, dopamine depletors, or, more rarely, associated with other drugs, such as calcium antagonists), and vascular parkinsonism are the most common forms of secondary parkinsonism [108]. Symmetric presentations and lack of the classical resting tremor are more frequent in these patients [109]. Although these conditions are more common among older subjects, they can be seen also in younger patients. When first evaluating a patient with EOPD, imaging studies of the brain should be considered to rule out rarer causes of secondary parkinsonism, such as vascular malformations (fistula, cavernoma, or arteriovenous malformations), single strategic lesions in the basal ganglia circuitry, supratentorial tumors or metastatic neoplastic lesions, as well as obstructive hydrocephalus [110]. Additional neurological symptoms can be frequently appreciated in secondary forms of EOPD and can help guide the diagnosis.

Systemic diseases that can present with parkinsonism in young age are represented by hepatic insufficiency (associated with bilateral hyperintensities of the basal ganglia on T1-weighted sequences or hyperintensities in the cerebellum and middle cerebellar peduncles on T2-weighted images), systemic lupus erythematosus (where characteristic serological biomarkers and systemic symptoms are crucial

for the diagnosis), as well as infectious diseases (such as HIV and possible opportunistic infections) [109]. A high number of cases of secondary parkinsonism were observed during the pandemic of Spanish flu [111].

The use of street drugs (such as amphetamines derivatives or MPTP), as well as exposure to carbon monoxide, manganese - as described in the paragraph “Metals in the brain” -, cyanide and methanol can represent additional causes of secondary parkinsonism in young patients [112].

A recent work also showed a correlation with sport-related head trauma and EO parkinsonism, in subjects where the most common genetic causes of EOPD were excluded [113]. Although more studies will be necessary to further clarify this association, traumatic brain injuries have been already correlated with parkinsonism, thus this trigger may be taken into consideration among the other factors as a causative or precipitating event for EO parkinsonism in predisposed subjects [114].

EO parkinsonism associated with additional characteristic features

EO parkinsonism and metals in the brain

Brain metal accumulation can manifest clinically as early-onset parkinsonism in several neurological disorders. Various metals can be accumulated in the brain and other body tissues in these conditions (e.g., copper in Wilson’s disease, iron in neurodegeneration with brain iron accumulation (NBIA), calcium in Fahr’s disease, and manganese in hypermanganesemia). Some of these disorders are genetically inherited, while others are acquired [115–118].

Typically, the clinical suspect for these conditions emerges after brain imaging studies (i.e., brain MRI for Wilson’s disease, NBIA, and hypermanganesemia, and head CT for brain calcifications) [119]. However, associated systemic findings, such as hepatic involvement in Wilson’s disease and hypermanganesemia, can be the first clue to suspect metal accumulation in the brain [115, 118, 120].

Wilson’s disease

Wilson’s disease is distributed worldwide, with an estimated prevalence of 1 case per 30,000 live births in most populations [146]. However, in some isolated populations, such as a small mountain village on the island of Crete, the prevalence is much higher (1 in 15 births), due to high rates of consanguinity [121].

Wilson's disease is an autosomal recessive disorder caused by loss-of-function mutations of *ATP7B* gene, which encodes for a copper-transporting ATPase which exports copper out of the cells, with a prominent role in the efflux of hepatic copper into the bile [122, 123]. The defective excretion of copper in the bile leads to hepatic copper overload and consequent damage, up to cirrhosis. Moreover, an impairment of copper incorporation into ceruloplasmin is also observed, resulting in low circulating levels of ceruloplasmin and elevated levels of unbound copper in plasma and urine. This altered copper metabolism leads to copper accumulation also in extrahepatic tissues, particularly in the basal ganglia [124]. In addition to the liver and brain, the cornea is also a characteristic site of copper deposition in Wilson's disease. Indeed, the pathognomonic sign of this disease is the Kayser-Fleischer ring, an annular deposition of copper in the periphery of the cornea [125].

Copper accumulation is associated with a progressive neurodegeneration of basal ganglia leading to a complex movement disorder often associated with bulbar symptoms. The movement disorder is usually characterized by tremor, dystonia, and/or parkinsonism. Bulbar symptoms consist of dysarthria, drooling and/or dysphagia. In addition, a range of additional neurologic features may be present, including cerebellar ataxia, chorea, hyperreflexia, seizures, cognitive impairment, and psychiatric features [115].

While parkinsonism is rarely found in isolation or as the predominant feature in Wilson's disease, this is commonly seen in combination with dystonia and/or tremor at presentation. Indeed, isolated parkinsonism occurs in less than 2% of neurologic presentations but parkinsonism in combination with other movement disorders is seen in the majority of the cases [115].

On brain MRI, T2 hyperintensity of the putamina and other deep brain nuclei is the most common abnormality. Involvement of the midbrain tegmentum can appear as a face of the "giant panda" on axial images. Axial T2 at the pons level may also show the face of a "miniature panda". On T1-weighted images, these same areas show hypointensity. However, patients with severe hepatic dysfunction show areas of T1 hyperintensity, especially in the globus pallidus, similar to that seen in acquired hepatocerebral degeneration attributed to manganese deposition [126].

Neurodegeneration with brain iron accumulation

NBIA is a heterogeneous group of inherited movement disorders characterized by abnormal iron

accumulation in basal ganglia and extrapyramidal movement disorders. The clinical features of NBIA range from global neurodevelopmental disorder in infancy to mild parkinsonism associated with minimal cognitive impairment in adulthood [116]. To date, ten NBIA genes have been identified, each associated with a different clinical syndrome and specific brain MRI features [118]. All forms of NBIA combined are considered to be ultra-rare with less than 1/1,000,000 affected world-wide, with the most common form being pantothenate kinase-associated neurodegeneration (PKAN), which accounts for approximately 50% of cases [127].

NBIA disorders presenting with parkinsonism as part of their clinical presentation include PKAN, *PLA2G6*-associated neurodegeneration (PLAN), beta-propeller protein-associated neurodegeneration (BPAN), mitochondrial-membrane protein-associated neurodegeneration (MPAN), Kufor-Rakeb Syndrome (KRS), Aceruloplasminemia, and Neuroferritinopathy [116]. EOPD is a frequent presentation of PLAN, BPAN, and KRS and typically shows atypical features, such as a poor levodopa response, lack of asymmetry, and the association with dystonia and pyramidal signs [116]. PLAN and KRS present brain iron deposition only in a subgroup of cases [128–130] and, therefore, are also classified in autosomal recessive forms of parkinsonism.

Mutations in *ATP13A2* (missense, nonsense, and frameshift) have been found in patients presenting with a form of autosomal recessive hereditary parkinsonism with juvenile onset before age 20, known as Kufor-Rakeb syndrome [131–134]. Cases with onset in adulthood have been described, with a mean age at onset of 24 [129]. The clinical spectrum encompasses severe parkinsonism of the akinetic-rigid type and various atypical manifestations, most characteristically ocular movement abnormalities (i.e., vertical supranuclear gaze palsy, slow vertical saccades), pyramidal signs, and facial-faucial-finger myoclonus [131, 135–138]. Intellectual disability, cognitive decline, hallucinations, dystonia, ataxia, and axonal neuropathy are also common [139]. Parkinsonism in Kufor-Rakeb syndrome has a moderate response to levodopa treatment, however levodopa-induced motor fluctuations occur early in the disease course [49, 131, 135] and response to levodopa is lost with disease progression [133]. Brain MRI findings include diffuse atrophy and a hypointense signal in the striatum and pallidum on T2-weighted images, demonstrating the accumulation of paramagnetic substances [49, 137, 138].

Mutations in *PLA2G6* have been associated with a form of parkinsonism-dystonia with onset between 10 and 30 years and with a rapid and severe progression to dementia (*PLA2G6*-associated Neurodegeneration or PLAN) [49, 140, 141]. Initial symptoms include psychiatric manifestations (i.e., depression, irritability, aggressive behavior, psychosis in some cases), gait changes with dragging of the foot and dysautonomia. Atypical features can include pyramidal signs, eye movement abnormalities (i.e., slow vertical saccades, nystagmus), optic atrophy, neuropathy, ataxia and cerebellar signs [135, 140–142]. Despite a modest response to dopaminergic agents, patients may develop early levodopa-induced dyskinesias. Brain MRI can show iron deposition in the cerebellum or in the pallidum, and cerebellar atrophy [49, 142]. Pontine atrophy with clival prominence can be seen in childhood-onset forms [143].

The clinical differential diagnosis among NBIA disorders is primarily based on the age at onset and on the different brain MRI features. PKAN, BPAN and MPAN typically have an early onset in childhood, PLAN and KRS begin in early adulthood, while neuroferritinopathy and aceruloplasminemia are adult-onset disorders [116]. Notably, BPAN-associated EOPD, due to mutations in *WDR45*, appears later in the course of the disease after intellectual disability and epilepsy which develop in childhood. MRI iron-sensitive sequences, such as susceptibility weighted imaging (SWI), gradient echo (GRE), and T2*, are needed to identify the characteristic hypointensity in specific NBIA disorders [144]. Concerning specific brain MRI changes of NBIA syndromes presenting with EOPD, the T1-weighted signal hyperintensity surrounding the substantia nigra is the hallmark of BPAN, the presence of associated cerebellar atrophy suggests a PLAN diagnosis, and marked atrophy and hypointensity of the globus pallidus in the initial phase is typical of KRS [144].

Fahr's disease

The presence of neurological and psychiatric symptoms associated with bilateral basal ganglia calcifications identifies a clinical syndrome defined as Fahr's disease [117]. This denomination mainly refers to idiopathic forms where no metabolic or other underlying causes are identified. Fahr's disease commonly affects people after their 40s; therefore, this disorder is not a frequent cause of EOPD. Patients are usually in good health in their youth and tend to develop symptoms later in adulthood

[145]. Calcifications are typically symmetrical and bilateral and involve the caudate, putamen, globus pallidus, thalamus, deep cortex, dentate nucleus, and, less frequently, the white matter [146]. CT scan is considered the gold standard for diagnosis identifying calcifications as hyperdense lesions [146]. Recently, mutations in five different genes (*SLC20A2*, *PDGFRB*, *PDGFB*, *XPR1*, and *MYORG*) were found to cause Fahr's disease, or, more precisely, Familial idiopathic basal ganglia calcification (FBGC). *MYORG*-related FBGC is the only autosomal-recessively inherited form, while the other four types are transmitted with an autosomal dominant pattern of inheritance [147]. Patients with early onset FBGC present frequently with psychiatric/cognitive symptoms or migraine, while older patients exhibit mostly movement disorders, among which parkinsonism is the most frequent presentation [117]. Parkinsonism can present with both motor and non-motor symptoms [148]. The motor symptoms include the cardinal signs of idiopathic Parkinson's disease (bradykinesia, rest tremor, rigidity, and postural and gait impairment) that tend to present symmetrically with the presence of coarse postural tremor. Levodopa response is variable from case to case. Parkinsonism can be associated with other movement disorders, such as choreoathetosis, non-parkinsonian tremor, dystonia, and orofacial dyskinesias. Associated neuropsychiatric symptoms consist of apathy, anxiety, depression, psychosis, and cognitive deterioration [117, 148].

Brain manganese accumulation

Manganese brain accumulation can be due to genetic or acquired causes. Genetically-determined brain manganese accumulations are ultra-rare conditions, with less than 100 cases reported world-wide so far [149]. There are two known genetic forms of brain manganese accumulation, associated with recessive mutations of *SLC30A10* and *SLC39A14* genes, but only the former can present as EOPD [118, 120]. Biallelic *SLC30A10* mutations are associated with a clinical syndrome characterized by movement disorders (e.g., dystonia and/or parkinsonism) resulting from manganese accumulation in the basal ganglia, hypermanganesemia, polycythemia, and liver disease (e.g., hepatomegaly with variable degree of hepatic fibrosis). Parkinsonism develops in early adulthood as shuffling gait, rigidity, bradykinesia, hypomimia, and monotone speech, and it is unresponsive to levodopa treatment. Other neurologic findings may manifest in childhood and precede

EOPD such as four-limb dystonia, leading to the characteristic “cock-walk gait”, dysarthria, and fine tremor. Hepatic failure, secondary complications of cirrhosis, and the neurologic disorder shorten life expectancy. Brain MRI T1-weighted images show characteristic hyperintensity of the basal ganglia, subthalamic nucleus, and dentate nucleus. Normalization of manganese blood levels with chelating therapies can improve brain MRI findings [120]. Differently, in *SLC39A14* deficiency, affected individuals present with hypermanganesemia and rapidly progressive childhood-onset parkinsonism-dystonia due to manganese deposition in the basal ganglia. Brain MRI appearances are the same as for *SLC30A10* disease. Distinguishing features are the absence of liver disease and polycythemia due to the lack of hepatic manganese deposition, which can be assessed by liver MRI [118].

Considering non-genetic forms, environmental exposure to high quantities of manganese is known to be neurotoxic and causes manganism, a clinical syndrome characterized by an extrapyramidal movement disorder (e.g., dystonia and/or parkinsonism) associated with T1 hyperintensity of the basal ganglia on brain MRI resulting from manganese accumulation in the basal ganglia. Manganism has been described in workers inhaling manganese-loaded dust or fumes (e.g., mining and welding industries), in individuals drinking manganese-contaminated water, and in drug addicts using intravenous drugs contaminated with potassium permanganate [150]. Brain accumulation of manganese is also observed in subjects with advanced hepatic cirrhosis or portosystemic shunts (acquired hepatocerebral degeneration) in which impaired biliary excretion of manganese results in manganese accumulation in the basal ganglia possibly causing debilitating movement disorders [151].

EO parkinsonism associated with metabolic conditions

A number of metabolic disorders can present with EO parkinsonism. Diseases caused by mutations in genes encoding for mitochondrial proteins are usually characterized by short stature, diabetes, ophthalmoplegia, deafness, cardiomyopathy, as well as neurological disorders such as myoclonus, seizures, and stroke like episodes [152]. The majority of the reports of parkinsonism and mitochondrial diseases consist of single case descriptions, as summarized in previous works [153, 154]. Although in most of these cases the neurological symptoms, including

parkinsonism, manifest during childhood, onset after the age of 21 year is possible. Thus they should be considered in the differential diagnosis of EOPD. Some of these conditions are described below (paragraph “EO parkinsonism associated with other neurological symptoms”). Matrilineal heritability, due to mutations of genes in the mitochondrial DNA, can be a key factor for suspecting these diseases.

Parkinsonism has also been reported in a growing number of conditions caused by impairment of the lysosomal/lipid metabolisms, such as Gaucher disease (GD) (as described in paragraph “Monogenic forms of EOPD”). Parkinsonism has been described in single cases of Niemann Pick type C (NPC), although screenings of large cohorts of patients with PD failed to confirm the association between mutations of the NPC-causative genes, NPC1 and NPC2, and PD. On the contrary, variants of the *SMPD1* gene, that is responsible for Niemann Pick types A and B, have been associated with PD across different populations [155–162]. NPC and GD are far more common among Ashkenazi Jews.

Chediak-Higashi syndrome (CHS) is a rare lysosomal disorder caused by mutations of the *LYST* gene and presenting with immunodeficiency, bleeding, lymphohistiocytosis, and oculocutaneous albinism. Few cases of EOPD with good response to levodopa have been found in carriers of homozygous mutations of this gene [151, 163–165]. Cerebrotendinous xanthomatosis (CTX) is due to mutation of the *CYP27A* gene which is involved in the cholesterol metabolism. CTX can frequently manifest with parkinsonism, in some cases as the presenting symptom, usually associated with other neurological manifestations, such as cerebellar ataxia and hyperreflexia (summarized in [166, 167]). CTX is more frequent in females, among Moroccan Jews and Druze in Israel (6/7,000 individuals) and in South and East Asia, compared with North America, Europe, and Africa [168].

Although the onset is more common during childhood, EOPD has also been reported in cases of gangliosidosis GM1, as well as late onset GM2 gangliosidosis (also called late onset Tay-Sachs disease, LOTS), and adult onset neuronal ceroid lipofuscinosis, usually in the context of additional neurological manifestations [15, 169–171]. Some of the conditions, such as LOTS, are more prevalent among Ashkenazi Jewish, although other clusters have been reported also within an Amish community in Pennsylvania and non-Jewish French Canadians in the area of St. Lawrence [172].

Parkinsonism can present in almost half of the cases of ataxia telangiectasia (A-T) (41% cases), usually in the second or third decade, when the other symptoms associated with this systemic disorder are already present (summarized in [173]). In a few cases levodopa has been reported to be beneficial in A-T.

Finally, young-onset parkinsonism can be present in the context of hemochromatosis, a hereditary condition caused by aberrant iron accumulation in the peripheral tissues causing, among the others, hepatic toxicity, anemia, diabetes, cardiac manifestations and hypogonadism [174–176]. In these cases, parkinsonism develops between the fourth and seventh decade and brain MRI usually shows hypointensity in the basal ganglia and substantia nigra [175, 176]. This condition is more frequent across people of Northern European descent, originally arising within the Celtic population [177].

EO parkinsonism associated with other neurological symptoms

Dystonia-parkinsonism syndromes

Parkinsonism may be part of the clinical spectrum of syndromes defined as “dystonia-parkinsonisms”. This term applies to rare conditions where the severity of dystonia usually equals that of parkinsonism. Unlike the parkinsonian syndromes with additional dystonia (i.e., *PRKN-PARK*), these conditions usually have their onset in childhood. The phenotype is often non-specific to a particular form and genetic investigations are required.

DYT-GCH1 typically presents with lower-limb dystonia, causing gait disturbance and a tendency to fall. Clinical features like diurnal fluctuation and sleep benefit are typically associated with this form and can be helpful in differentiating it from other forms of EOPD. The response to levodopa of both dystonic and parkinsonian signs is remarkable with low-doses (i.e., <300–400 mg/daily) [178] with no development of the levodopa-induced dyskinesias.

Mutations in protein kinase, interferon-inducible double-stranded RNA-dependent activator (DYT-PRKRA) cause an autosomal recessive form of young onset, progressive generalized dystonia and mild parkinsonism [179]. A remarkable involvement of oromandibular and bulbar regions with a sardonic smile, tongue protrusion, significant speech and swallowing disturbances is typical of this form. The axial involvement of the neck and trunk can lead to opisthotonic postures. Parkinsonism is usually not a prominent feature, appears later than dystonia and is

characterized by bradykinesia and rigidity, rather than resting tremor. The disorder was initially described in three Brazilian families [179]. In a few cases, bilateral striatal degeneration has been observed on brain MRI [180, 181]. However, the three described cases presented with a very young age of onset, before the age of 20 [180, 181].

Rapid-onset dystonia parkinsonism (RODP) due to mutations in the *ATP1A3* gene (*DYT-ATP1A3*) is characterized by an abrupt onset of dystonia and parkinsonism over minutes to several weeks, usually triggered by febrile illness, physical or emotional stressors, alcoholic binges, or childbirth [182, 183]. The acute onset of symptoms and the autosomal dominant mode of inheritance are distinctive features of *DYT-ATP1A3* that can help distinguish this form from other conditions. Age at onset is typically in the second to third decade of life. Initial symptoms rapidly evolve over weeks and then stabilize over time. A possible second abrupt worsening of symptoms after years is possible [184]. The rostrocaudal gradient of involvement with prominent dysarthria and hypophonia, and the asymmetric distribution of both dystonia and parkinsonian features is typical. Tremor is usually absent. Levodopa treatment is ineffective [185].

DYT-TAF1 is an adult-onset X-linked recessive neurodegenerative disorder, affecting predominantly men (male to female ratio of 93:1), described in patients from the island of Panay, Philippines, and very rarely in the general population [186, 187]. Dystonia is usually focal at onset, involving the cranio-cervical region with retrocollis, oromandibular dystonia, blepharospasm, and tongue protrusion, and it has a tendency to generalize as the disease progresses [188]. Deep brain stimulation of the internal pallidum (GPi-DBS) has proven effective with long-lasting benefit, especially when performed in the early stage of the disease [189, 190]. Ten years after the onset there is usually a decrease in the severity of dystonia and parkinsonism becomes gradually more prominent [188, 191]. This temporal pattern is quite unique and helps differentiate this condition from other disorders where there is a progression of both dystonic and parkinsonian features.

Parkinsonism-ataxia

Parkinsonism may be part of the clinical presentation of a range of spino-cerebellar ataxias (SCAs) associated with polyglutamine expansion (SCA1, 2,3,6,7,8,10,12,17), other SCAs (19,21,22,28), and Fragile-X tremor ataxia syndrome (FXTAS)

[192–194]. Characteristic features of the underlying disease (i.e. mental retardation, physiognomic features (long face, low set ears), action tremor in FXTAS; slow saccades in SCA2; pyramidal signs in SCA3; macular degeneration in SCA7; dementia, psychiatric features, chorea in SCA17; seizures in SCA10; cognitive impairment in SCA21; ophthalmoparesis, ptosis, spasticity in SCA28) can sometimes be overlooked by physicians but they are important to guide the diagnosis [195, 196]. SCA1, 2, 3 and 17 should be suspected in patients presenting with a phenotype suggestive of multiple system atrophy (MSA), as they can present with prominent parkinsonism and dysautonomia, although the classical “hot cross bun” sign on brain MRI, that is characteristic of MSA, is only rarely present in these forms [197].

Parkinsonism, PEO, or optic atrophy

Parkinsonism preceded by development of progressive external complete ophthalmoplegia (e.g., on both horizontal and vertical plane) has been reported in a few cases of subjects carrying mutations in the mitochondrial-related genes *TWINK* and *POLG1* [198, 199]. In these cases, parkinsonism may not be prominent and thus be overlooked. A variable phenotypic presentation and penetrance were present in the reported families. SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis) syndrome has been reported as well in subjects with parkinsonism due to *POLG1* variants [200]. *POLG1* mutations can be found also in cases of parkinsonism associated with optic atrophy, manifesting with a gradual vision loss, as well mutations of the *SLC25A46* [201].

Parkinsonism and spastic paraplegia

Mutations in the *SPG11* gene have been identified to be a major cause of autosomal recessive hereditary spastic paraplegia (SPG) with thin corpus callosum. Juvenile-onset symmetric parkinsonism has been described, with variable response to dopamine intake [202, 203].

Other SPG syndromes may display parkinsonism as part of the clinical picture, in particular in SPG7 [204–206] and SPG15 [207, 208].

Parkinsonism and intellectual disability

Monogenic forms of early intellectual disability and early or juvenile onset parkinsonism have been described. The combination of early-onset parkinsonism and intellectual disability is a distinctive feature of patients with mutations in *RAB39B* [209] and

PTRHD1 [210, 211]. Intellectual disability develops over a spectrum which encompasses delayed speech initiation, early learning difficulties, and obsessional and ritualistic behavior in childhood [212]. It is non-progressive and can be mild, and therefore is often neglected. Intellectual disability typically precedes the onset of parkinsonism, which has been described to occur as early as age 10 in males with *RAB39B* mutations [209] and in the 3rd-4th decade in patients with mutations in *PTRHD1* [213]. *RAB39B* mutations (point mutations, deletions, and duplications) are the only known cause of PD with X-linked inheritance [30]. Affected females with mutations in *RAB39B* have a later onset of parkinsonism and a less severe phenotype [214]. Unaffected females with heterozygous *RAB39B* mutations have also been reported [214]. The clinical phenotype is that of typical parkinsonism with tremor at rest, bradykinesia and rigidity, and a good response to levodopa. Atypical features have been described in both *RAB39B* (i.e., postural tremor, seizures, macrocephaly, autism spectrum disorder and strabismus) [215–217] and *PTRHD1* (i.e., pyramidal signs, distal muscular atrophy and hyposthenia, axonal sensorimotor polyneuropathy, hypersomnia, hypersexuality) [210, 213, 218]. Basal ganglia calcifications can be seen in *RAB39B*-related EOPD [209, 219], whereas brain MRI is normal in *PTRHD1* mutations.

Phenotypes associated with mutations in *WDR45* have already been discussed (“Neurodegeneration with brain iron accumulation” paragraphs).

A dopamine-responsive parkinsonian syndrome has been reported in patients with mutations in the *PPP2R5D* gene associated with a rare autosomal-dominant disease with developmental delay and mild to severe intellectual disability [220–223].

Interestingly, a recent review found that impaired cognition or neuropsychiatric disorders are also an early presentation in 92% of patients with EOPD associated with mutations in *ATP13A2*, *PLA2G6*, or *FBXO7*, suggesting that these may occur early before parkinsonism develops [224].

Parkinsonism and seizures

Seizures with onset in infancy or childhood are seen in ~50% [224] of patients with parkinsonism associated with mutations in *DNAJC6* [88, 225, 226] and *SYNJ1* [227–229]. Onset of parkinsonism, often associated with dystonia, ranges between 7 and 42 years in patients with *DNAJC6* mutations [88, 226] and occurs between 20 and 40 years in *SYNJ1* carriers [227]. Pyramidal signs and rapid

progression to dementia are often seen in *DNAJC6* [88, 225], whereas *SYNJ1* patients can present with eyelid apraxia and supranuclear gaze palsy [227, 230]. Reports on brain imaging describe generalized atrophy in *DNAJC6* and *SYNJ1* cases and T2 hyperintensity in the posterior white matter and substantia nigra of few *SYNJ1* patients [227, 228].

HOW TO APPROACH A PATIENT WITH EO PARKINSONISM

Clinical history

A detailed clinical history can provide important information to reach a diagnosis in patients presenting with EO parkinsonism. An initial presentation of pure parkinsonism within the 3rd decade, with no prominent additional clinical manifestations, is more characteristic of monogenic forms of PD (such as *PARK-PRKN*, followed by *PARK-PINK1* and *PARK-DJ1*). Complicated forms where parkinsonism coexists with pyramidal symptoms, other movement disorders (mostly dystonia or cerebellar features), cognitive or psychiatric manifestations and an earlier age of onset are more suggestive of mutations of *ATP13A2*, *PLA2G6*, *FBXO7*, *RAB39B*, *PTRHD1*, *GCH1*, *ATP1A3*, Wilson's disease, NPC and NBIA. Later age of onset, in the fourth or fifth decades, is more suggestive of mutation of the *GBA* gene, CTX, SCA (2, 3, 17), occasionally of mutations of the *LRRK2* gene, as well as secondary forms such as drug-induced parkinsonism, or parkinsonism-related to systemic conditions.

Certain clinical features are very suggestive of specific forms of EO parkinsonism (Fig. 1). For example, epilepsy can be associated with *SYNJ1* mutations or mitochondrial diseases. Cognitive impairment or developmental delay present early in Kufor-Rakeb syndrome, Fahr's disease, *PPP2R5D*-related parkinsonism, while they can be a later manifestation of CTX and Wilson's disease. Psychiatric features can be the initial manifestations of NPC, LOTS and Westphal syndrome, and they can complicate Fahr's disease, Wilson's disease, and SCA17 as the disease progresses, or can be consistent with a diagnosis of parkinsonism due to the use of dopamine blocking agents. Systemic symptoms are more characteristic of mitochondrial disorders (such as deafness, diabetes, lipomatosis), NBIA and hemochromatosis (diabetes and hepatotoxicity), NPC or GD (hepatosplenomegaly), history of diarrhea or early-onset cataracts in CTX, and the characteristic combination

of hematological, immune and oculocutaneous manifestation in the CHS.

Because of the possibility of preventing severe complications when this condition is recognized and promptly treated, genetic analysis of *ATP7B* gene for the diagnosis of Wilson's disease should be performed in any patient presenting with parkinsonism in childhood, adolescence or early adulthood, in particular when parkinsonism is subacute or rapidly progressive and associated with concomitant dystonia and/or dysarthria. In addition, the presence of the Kayser-Fleischer ring (observed in most neurologic cases) and evidences of liver disease (e.g., jaundice, unexplained cirrhosis, thrombocytopenia or coagulopathy) should immediately raise the diagnostic suspect of Wilson's disease [231].

EOPD is usually slowly progressive. On the contrary, abrupt onset can be suggestive of RODP, viral, immune-mediated, or vascular (stroke, cavernomas or arteriovenous malformations) conditions. While acute forms usually have a more static presentation, the majority of the other forms of EO parkinsonism are progressive, especially the more complicated ones (such as NBIA, Fahr's disease, and metabolic conditions) compared with pure monogenic forms of parkinsonism (such as *PARK-PRKN*, *PARK-PINK1*, *PARK-DJ1*) or *DYT-GCH1*. Very low doses of levodopa or dopamine agonists are able to provide a significant relief of symptoms in patients with *PARK-PRKN*, *PARK-PINK1*, *PARK-DJ1* and *DYT-GCH1*. However, these patients, except for *DYT-GCH1*, will soon present motor fluctuations and levodopa-induced dyskinesias. On the contrary, the other forms of EO parkinsonism are poorly responsive to dopaminergic medications compared with iPD.

Non-motor symptoms can also help discriminating among different causes of EO parkinsonism. Symptoms such as dysautonomia, RBDs, hyposmia, which are typically found in patients with iPD, are much rarer, if not absent, in the majority of patients with EOPD. Their prominent presentation can be associated with mutations of the *GBA* gene. Dysautonomia and RBD can also be found in NPC and in some cases of SCA (2,3,17).

As part of the assessment of the clinical history, a detailed investigation of patients' family history is mandatory, especially in the context of genetic forms. If family history suggests an autosomal dominant pattern of inheritance, genetic screening should include *GBA* (high prevalence, low penetrance), *LRRK2* (medium-high prevalence, low penetrance), and *SNCA* (low prevalence, high penetrance).

If consanguinity is present in the family and other family members (e.g., siblings) are affected by EOPD, then *PRKN*, *PINK1*, and *DJ-1* are the most probable cause; if negative, other genes related to recessive forms can be considered (*PLA2G6*, *FBXO7*, *ATP13A2*, *DNAJC6*, *SYNJ1*, *VPS13C*, *PTRHD1*, *ATP7B*) [232].

Finally, patients' ancestry should always be inquired, since some genetic mutations associated with EO parkinsonism present high prevalence in selected ethnic groups. For example, the *LRRK2* G2019S mutation is a frequent cause of PD among North Africans, Ashkenazi Jews, and in the Mediterranean basin (e.g., Italy, Spain, and Portugal). Other population-specific *LRRK2* mutations are the R1441G in Basques and the R1441C in Belgians and Southern Italians. Another example is the *GBA* N370S mutation, which is distributed worldwide, but presents a particular enrichment in Ashkenazi Jews [232].

Clinical exam

When approaching a patient with EOPD, a comprehensive clinical examination is essential to collect all elements that will aid in the diagnostic process. While the classic onset of iPD is in one body part or hemi-body, the initial presentation of EO parkinsonism observed in forms of NBIA and in Fahr's disease is often symmetric and involves both halves of the body equally since the first stages. Similarly, acquired parkinsonisms due to exposure to dopamine-blocking agents and to vascular lesions in the basal ganglia typically have a symmetric presentation. Some forms of EO parkinsonism exhibit a characteristic distribution and preferential involvement of the limbs or the cranial district. *DYT-GCH1*, *PARK-FBXO7*, and vascular parkinsonism typically are more predominant in the lower limbs, while oromandibular involvement and bulbar signs are frequent in Wilson's disease, *DYT-PRKRA*, *DYT/PARK-ATP1A3*, *DYT-TAF*. The classical distinction between tremor-dominant and akinetic-rigid phenotypes helps guide the clinical reasoning. Predominant rigidity and bradykinesia are frequently seen in *PARK-ATP13A2*, dystonia-parkinsonism (e.g., *DYT-PRKRA*, *DYT/PARK-ATP1A3*), as well as in drug-induced and vascular parkinsonism, whereas a tremor-dominant phenotype (rest, postural, or kinetic tremor) can point to a different etiology (Wilson's disease, Fahr's disease, *PARK-LRRK2*). A careful examination of ocular movements in all its components is critical, considering the

velocity of the saccades (reduced in *PARK-ATP13A2*, NBIA/*DYT/PARK-PLA2G6*, *PARK-FBXO7*, and *SCA2*), gaze limitation (vertical gaze palsy in *PARK-ATP13A2*, NPC, A-T, *PARK-SYNJ1*), and ophthalmoplegia (mitochondrial disorders). Close inspection of the eyes can also show peculiar features, such as Kayser-Fleischer rings in Wilson's disease and oculocutaneous albinism in CHS.

Additional movement disorders and neurological signs can accompany parkinsonism in several cases. Dystonia is characteristic of forms of monogenic EOPD (*PRKN*, *PINK1*, *PLA2G6*), dystonia-parkinsonism, and NBIA, as well as Wilson's disease and hypermanganesemia. Chorea and choreoathetosis can be observed in Fahr's disease, Wilson's disease, A-T, and most forms of NBIA. The association of parkinsonism and pyramidal signs may be indicative of specific phenotypes, most notably the ones associated with variants of *FBXO7*, *ATP13A2*, *PLA2G6*, *DNAJC6*, *PRKN*, *PINK1*, *RAB39B*, *PTRHD1*, *VPS13C*, forms of NBIA, and CTX. Myoclonus can be seen in a minority of cases of EOPD, including *PARK-ATP13A2* (facial-facial-finger mini-myoclonus), *PARK-SNCA*, and mitochondrial cytopathies. Ataxia and cerebellar signs may be observed in *PLA2G6*-related parkinsonism, CTX, AT, NPC, SCAs, and FXTAS.

Imaging studies

Specific neuroradiological signs may strongly suggest the genetic diagnosis. For example, the T2*/SWI hypointensity of basal ganglia is a key feature of NBIA. The presence of basal ganglia calcifications on CT scan should address the genetic investigation to the FBGC forms. T2-hyperintensity of the putamina and other deep brain nuclei are the most common abnormality seen in Wilson's disease. T2-hyperintensity of the white matter in the dentate nuclei, cerebellar peduncles, and internal capsule, substantia nigra, globus pallidus, striatum is found in CTX. Conversely, T1-hyperintensity of the basal ganglia can indicate manganese accumulation. Metabolic forms, such as NPC, CHS, and A-T can instead present cortical and cerebellar atrophy, particularly in advanced stages of the disease. A detailed description of specific MRI neuroradiological features associated with each form is reported in Table 1. All forms of Parkinson's disease and the vast majority of degenerative parkinsonisms are associated with a reduction of the dopaminergic transporter (DaT) at the presynaptic dopaminergic terminal, as shown by dopaminergic

functional imaging (e.g., Ioflupane I 123 SPECT) [233]. Fahr's disease, hereditary spastic paraplegias, and spinocerebellar ataxias can be associated with abnormalities of the presynaptic dopaminergic terminal, more frequently if clinical parkinsonism is present. Differently, parkinsonian disorders associated with brain manganese accumulation (acquired or inherited) and non-degenerative dystonias display a normal Ioflupane I 123 SPECT imaging [234, 235]. A summary of functional imaging features of early-onset parkinsonisms is reported in Supplementary Table 1.

GENETIC COUNSELING

Next generation sequencing (NGS) panels or diagnostic exome sequencing represent the best diagnostic approach in the absence of strong candidate genes. With these techniques, all genes related to EOPD and EO parkinsonism are sequenced simultaneously, which is a cost and time effective method to identify possible mutations. Shortcomings related to this approach include a low sequence efficiency for difficult-to-sequence DNA regions and the risk of missing gross structural alterations. Each variant identified by gene panels should be confirmed by the Sanger approach. Moreover, dosage assay techniques (i.e., Multiplex Ligation-dependent Probe Amplification (MLPA) and qPCR) should always be implemented when analyzing *SNCA*, *PRKN*, *PINK1*, and *DJ-1* genes in order to detect rearrangements that can be missed by NGS, especially heterozygous deletion or duplications. It is noteworthy that the interpretation of NGS results, which often leads to the detection of variants of unknown significance (VUS), requires the expertise of a neurogeneticist specialized in movement disorders. Additional studies are mandatory in case novel genetic variants are detected in order to confirm their pathogenetic role [232].

As an alternative approach, each single gene can also be analyzed by classic Sanger sequencing, a highly reliable but expensive technique, that can be used as a first approach only when few candidate genes are suspected as causative. Sanger sequencing should always be complemented with dosage assay techniques. Pathogenic mutations of *LRRK2* gene have been found in exons 29-30-31-34-35-41-48, therefore only these exons should be analyzed for clinical purposes.

Genetic counseling of patients with EOPD involves the entire family. Whether genetic testing

should be offered to asymptomatic family members is still very controversial. Except for genetic forms in which a disease-modifying therapeutic approach exists (e.g., Wilson's disease) and an early genetic diagnosis can be useful to the patient, no defined guidelines are available for genetic counseling of family members of patients with EO parkinsonism.

The identification of causative genes of EOPD and EO parkinsonism contributed to increase our understanding of the genetic architecture and pathogenic mechanisms of these conditions. These discoveries led to the selection of targeted drugs for specific genetic forms (e.g., *GBA*- and *LRRK2*-related forms). At present, clinical trials testing these potential therapeutic approaches are ongoing [236].

CONCLUSIONS

EO parkinsonism can be the manifestation of a broad range of conditions. A prompt and accurate diagnosis is crucial for counseling of these patients, prognostic implications, and possibly early treatments to prevent further complications, such as in the case of Wilson's disease. Specific genetic mutations can be more difficult to distinguish only based on phenotype in case of monogenic forms of EOPD, because of the extensive overlap of their clinical presentation. On the contrary, complicated, and rarer forms related to genetic and metabolic conditions, or metals deposition in the brain can be more easily differentiated, because of the characteristic clinical features, radiological and laboratory findings. Although rare, awareness of the different forms of EO parkinsonism by movement disorder specialists will certainly improve the management and care of these patients.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JPD-212815>.

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