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Review article

Juvenile parkinsonism: Differential diagnosis, genetics, and treatment

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ABSTRACT

Juvenile parkinsonism is arbitrarily defined as parkinsonian symptoms and signs presenting prior to 21 years of age. Levodopa-responsive juvenile parkinsonism that is consistent with diagnostic criteria for Parkinson's disease is most often caused by mutations in the PARK-*Parkin*, PARK-*PINK1*, or PARK-*DJ1* genes. However, many other genetic and acquired parkinsonian disorders presenting in childhood or young adulthood are being reported, often with atypical features, such as presence of other movement disorders, cognitive decline, and psychiatric symptoms. The genetic landscape of juvenile parkinsonism is rapidly changing with the discovery of new genes. Although the mainstay of treatment remains levodopa, other symptomatic therapies such as botulinum toxin for focal dystonia, supportive medical therapies, and deep brain stimulation in select cases, may also be used to provide the most optimal long-term outcomes. Since the topic has not been reviewed recently, we aim to provide an update on genetics, differential diagnosis, evaluation, and treatment of juvenile parkinsonism.

1. Introduction

Parkinsonism is characterized by bradykinesia and at least one of rest tremor or rigidity [1], but there are often many associated motor and non-motor features. The frequency of parkinsonism varies depending on the diagnostic criteria, population studied, and methods of ascertainment. In one study based on a United States population, the incidence of parkinsonism was 0.8 per 100.000 person-years in the 0–29 year age group and 3.0 per 100.000 person-years in the 30–49 year age group [2]. Meta-analysis of 47 studies found that the prevalence of Parkinson's disease (PD), the most common form of parkinsonism, rises from 0.04% for ages 40–49 years to 1.1% in 70–79 years [3]. Several studies have suggested that the incidence of parkinsonism and PD has been increasing over the past several decades and PD is now the fastest growing neurological disorder [4]. While the incidence of PD increases sharply with age it is still rare in the young and it is estimated that less than 5% of PD cases present prior to age 50 years [3,5,6].

Early-onset parkinsonism is defined as onset of parkinsonism of any cause at age 40 years or younger, although some have defined the upper age limit as 50 years [7]. Juvenile parkinsonism (JP) is arbitrarily defined as parkinsonian symptoms and signs with onset before age 21 years and young-onset parkinsonism when onset is between 21 and 40 years of age [8–12]. Similarly, early-onset PD (EOPD) is subdivided into juvenile PD (JPD) and young-onset PD (YOPD).

Neuropathologically, PD is characterized by the presence of Lewy body (LB) pathology and loss of pigmented neurons in the substantia nigra pars compacta (SNpc) [13–15]. However, LB pathology is not specific to PD and an absence of LB pathology may be seen in several genetic types of typical parkinsonism which without genetic testing would be indistinguishable from idiopathic PD [16].

JP is a rare, heterogenous, and commonly familial syndrome [8]. Most patients do not meet the clinical or pathological criteria for PD as they often present with atypical features, such as disproportionate severity of another movement disorder (e.g. dystonia, ataxia, spasticity), early cognitive decline, severe behavioral disturbance, or relevant medical history such as exposure to dopamine receptor blocking agents (DRBA), head trauma, brain tumor, and other secondary causes [1,8–10]. Levodopa-responsive JP is most often caused by parkin mutations [17], but many other genetic causes should be considered in the differential diagnosis of JP, including Huntington's disease (HD), Wilson's disease (WD), and dopa-responsive dystonia (DRD) (Table 1). Idiopathic PD rarely occurs occur in the juvenile population, although LB pathology has been reported in some cases of JP examined at autopsy [18–20], including genetic forms of JP [16]. Conversely, most patients with YOPD are clinically and pathologically indistinguishable from patients with late-onset PD. In a cohort of 149 patients with EOPD seen in a tertiary referral center, 10 had JPD without atypical features and slow progression [12]. Of these, 4 with JPD had been reported

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previously [11]. The median age at onset was 17 years (range, 5–19) and 50% had at least 1 first- or second-degree family member with parkinsonism (all with onset < age 40 years). Nine of 10 patients had a good or excellent initial response to levodopa, although this was complicated by levodopa-induced dyskinesias and motor fluctuations within 6 months (median) from start of therapy. In another series of 6 patients with levodopa-responsive JP with mean age at onset of 12.5 years (range, 7–19) all patients had atypical features, including ophthalmoparesis (4/6), epilepsy (3/6), myoclonus (1/6), and other neurological symptoms [21].

Since the most recent review of JP, published about a decade ago [10], multiple new genetic mutations have been described and additional information has accumulated about previously known mutations [17,22–24]. Therefore, the primary goal of this review is to provide an update on genetics, differential diagnosis, evaluation, and treatment of JP.

2. Etiology of juvenile parkinsonism

2.1. Genetics

Monogenic forms of parkinsonism will preferentially be referred to by their specific affected gene rather than the traditional "PARK" nomenclature as suggested by the Movement Disorders Task Force [25]. In general, if a patient with JP is indistinguishable from a patient with idiopathic PD (iPD), except for age at onset, then the clinician should primarily suspect (in order of frequency) a diagnosis of either PARK-*parkin*, -*PINK1*, or -*DJ1*. The presence of atypical features, such as predominance of other movement disorders (e.g. dystonia, chorea, myoclonus, ataxia, spasticity), mood, or cognitive problems, may indicate other genetic (e.g. HD) or acquired disorders (e.g. medication exposure or acquired developmental or structural brain or spinal cord problems) and guide evaluation accordingly. Fortunately, genetic testing for several inherited parkinsonian disorders is now readily available, even outside a research setting, although it is not easily accessible because of high cost [26]. Of course, genetic testing should be always combined with appropriate counseling [27]. Table 1 lists genetic disorder described in section 2.1 that may be associated with JP.

2.1.1. Autosomal recessive typical juvenile parkinsonism

These disorders will generally conform to the diagnostic criteria for PD [1].

2.1.1.1. PARK-parkin (PARK2). Parkin is an E3 ubiquitin ligase which plays a critical role in the induction of mitophagy after oxidative stress [28]. Loss of the ubiquitin ligase effect in *parkin* gene mutations leads to accumulation of oxidative damage which leads to cell damage, especially in cells with high mitochondrial activity including neurons and cardiac myocytes. *Parkin* gene mutations were first reported in a consanguineous Japanese family [29] and accounts for an estimated 10–20% of EOPD cases [30]. PARK-*parkin* represents a large proportion of cases otherwise classified as JPD based on age at onset [7,31]. In two multicenter studies with more than one thousand EOPD patients, the frequency of (homozygous or compound heterozygous) PARK-*parkin* (age group) was 35–77% (0–20 years), 17–26% (21–30 years), and 2–3% (31–40 years), respectively [7,31]. However, the median age at onset of PARK-*parkin* is 31 years (range, 3–81 years) with juvenile onset (< 21 years) in just 19% [32].

Parkin mutations have also been found to co-occur in some cases of progressive supranuclear palsy [33], restless legs syndrome [34–36], and essential tremor [37,38] although this finding does not imply causation.

Bradykinesia, a required sign for the diagnosis of PD [1], is the most frequently reported sign overall in PARK-*parkin*, followed by tremor (particularly in the legs), rigidity, dystonia, and postural instability [17]. Other common features include sleep benefit, diurnal fluctuations, and hyperreflexia. Atypical features (e.g. anterocollis, spasticity, upper motor neuron signs) and cognitive decline have each only been reported in approximately 3% of cases [17]. Features reported with PARK-*parkin* include presentation with dystonic gait, hemiparkinsonism-hemiatrophy, dysautonomia, and peripheral neuropathy.

Although the most common initial sign of PARK-*parkin* is bradykinesia [32], 42% of patients reported that dystonia was one of their initial signs in one report [31]. Onset with action-induced, lower limb dystonia with diurnal fluctuation may lead to diagnostic delay [39] or misclassification as DRD [40,41] and sometimes as paroxysmal exercise-induced dystonia [42]. Only few patients exhibit cognitive decline and olfaction is often preserved in PARK-*parkin* compared to iPD [17,43–45].

The clinical course is generally benign with slow progression [46] and excellent response to levodopa, but with early development of motor fluctuations and levodopa-induced dyskinesias in the majority of patients [42].

It is generally not possible to distinguish between PARK-*parkin*, PARK-*PINK1*, and PARK-*DJ1* on clinical grounds alone due to marked clinical overlap and a high degree of missing data in reported cases (7–78% for cardinal motor signs) [17].

Pathologically, PARK-*parkin* is characterized by loss of neurons in the SNpc, but the dorsal tier is usually preserved. In contrast there is usually minimal or no neuronal loss in locus coeruleus (LC) and dorsal nucleus of vagus, raphe nucleus, or nucleus of Meynert. LB pathology is absent in two thirds of the examined brains of patients with homozygous or compound heterozygous parkin mutations [16], including in a single case with juvenile onset [47]. Compared to PARK-*parkin,* heterozygous (single) *parkin* mutation carriers with late-onset parkinsonism commonly have LB pathology, which makes it likely that the mutation is not causative in those subjects [16].

Presynaptic, striatal, dopaminergic imaging demonstrates more severe and relatively symmetric signal loss in PARK-*parkin* compared to non-*parkin* EOPD patients [48–50]. Interestingly, presynaptic nigrostriatal dysfunction has also been demonstrated in asymptomatic *parkin* mutation carriers [51].

2.1.1.2. PARK-PINK1 (PARK6). PINK1 (PTEN-induced putative kinase 1) is recruited to mitochondria during oxidative stress and phosphorylates parkin which then becomes activated from its native autoinhibited state ("PINK1-parkin-dependent mitophagy") [28]. Mutations in the *PINK1* gene were first described as a cause of AR typical parkinsonism in three consanguineous families from Italy and Spain [52]. PARK-*PINK1* is the second most common genetic mutation in EOPD accounting for an estimated 2–7% of cases [30]. The median age at onset of PARK-*PINK1* is 32 years (range, 9–67 years) with juvenile onset in 15% [17]. As with *parkin* mutations, it is controversial if heterozygous (single) *PINK1* mutations increase the risk of PD [53,54]. However, Puschmann and colleagues (2017) recently provided convincing evidence that a specific *PINK1* mutation (p.G411S) decreases the activity, but not the protein level, of wild-type *PINK1* in a dominant-negative fashion [55].

Clinically, PARK-*PINK1* appears to be indistinguishable from PARK-*parkin* with respect to presentation and course [17,43]. Some reports suggest that non-motor symptoms are more common in PARK-*PINK1* compared to PARK-*parkin* [53,54], including a higher frequency of anosmia [56].

Knowledge of the pathological features of PARK-*PINK1* is limited to three case reports, one with young-onset parkinsonism [57] and two with typical (> 50 years) onset of PD [58,59]. Neuronal loss in the SNpc was noted in all cases. LC neuron loss was not reported in two cases [57,58] and was mild in the third case [59]. The most striking difference between the cases is with regard to the distribution of LB pathology which involved the SNpc, brainstem reticular nuclei, and nucleus basalis of Meynert in the case with young-onset parkinsonism

[57], but was restricted to the amygdala [58] or absent, except for Lewy neurites (LN) in the olfactory nerve [59], in the other cases.

MRI brain is usually normal and functional imaging reveal relatively symmetric presynaptic, nigrostriatal, dopaminergic signal loss in PARK-*PINK1* [48,49].

2.1.1.3. PARK-DJ1 (PARK7). The oncogene *DJ1* protects against damage from oxidative stress and may act in a parallel pathway to that of parkin and *PINK1* [60]. Mutations in *DJ1* were first described in consanguineous European families [61]. Of the three main types of autosomal recessive typical parkinsonism (PARK-*parkin*, -*PINK1*, and -*DJ1*), PARK-*DJ1* is the least frequently reported [17,43], accounting for an estimated 1–2% of EOPD cases [30]. The median age at onset of *PARK-DJ1* is 27 years (range, 17–40 years) with juvenile onset in 13% [17].

Clinical and neuroimaging features of PARK-*DJ1* are similar to PARK-*parkin* and PARK-*PINK1*. However, non-motor symptoms have been reported considerably more frequently in PARK-*DJ1* (57%) compared to PARK-*parkin* (13%) and PARK-*PINK1* (42%) [17,43].

Autopsy studies have described neuron loss in the SNpc and LC, and widespread LB pathology was noted in the brain of one patient with a novel homozygous *DJ1* mutation [62]. However, the patient exhibited atypical clinical (e.g. poor response to levodopa and progressive upper motor neuron signs) and pathological (e.g. axonal spheroids) features. Mutation status of other relevant genes (e.g. PLA2G6) [16] was not reported. The findings may not be generalizable to other patients with *DJ1* mutations. Alpha synuclein deposition in skin is characteristic of iPD and was recently demonstrated in a patient with homozygous *DJ1* mutations [63], which may serve as a distinguishing feature compared to PARK-*parkin* and atypical parkinsonisms [64]. MRI is usually normal and dopaminergic imaging is abnormal in PARK-*DJ1* [63], similar to PARK-*parkin* and –*PINK1*.

2.1.2. Autosomal recessive atypical parkinsonism

In this section we review disorders that are characterized primarily by parkinsonism in addition to other neurologic features (e.g. upper motor neuron signs). Several disorders often described as “parkinsonian-pyramidal syndromes” may have juvenile onset and some of these will be reviewed in section *2.1.4 Other monogenic disorders*. These disorders have also been reviewed extensively elsewhere [22].

2.1.2.1. PARK-ATP13A2 (PARK9; Kufor-Rakeb syndrome). *ATP13A2* encodes a lysosomal 5 P-type ATPase involved in cellular manganese homeostasis [65]. Phenotypic expressions of *ATP13A2* mutations include PARK-*ATP13A2, h*ereditary spastic paraplegia (HSP), amyotrophic lateral sclerosis (ALS), and neuronal ceroid lipofuscinosis [66,67]. PARK-*ATP13A2* is a form of autosomal recessive JP, often associated with dystonia, eye movement abnormalities (supranuclear gaze palsy, slowed saccades, oculogyric spasms), facial-faucial-finger minimyoclonus (brief jerking movements of the face, pharynx, and fingers), upper motor neuron signs, psychosis, and dementia [32,68–70]. Onset is earlier than age 20 years in the vast majority of patients (> 80%) [32]. The most frequently reported initial symptom is bradykinesia followed by cognitive decline/intellectual impairment [32]. Early development is often normal [69,71], although some patients have had cognitive impairment preceding onset of motor symptoms [72,73]. Dementia and psychosis is seen in most cases with sufficiently advanced disease [69,70,72].

Treatment with levodopa is associated with excellent control of parkinsonism which may allow a return to functional independence at least for a few years, until disease progression and treatment-related complications (motor fluctuations and levodopa-induced dyskinesias) renders the patient bed- or wheelchair-bound and dependent on others [69,71,72]. A good response to anticholinergics has been reported in some cases [72,74].

Imaging shows evidence of global cerebral atrophy [69,71,72,75], some exhibit striatal iron deposition [72], and striatal dopaminergic denervation in most cases [73,75,76].

2.1.2.2. DYT/PARK-PLA2G6 (PARK 14). Phospholipase A2, encoded by *PLA2G6*, plays a critical role in cell membrane phospholipid homeostasis [77]. The main phenotypes associated with *PLA2G6* mutations are *PLA2G6*-associated neurodegeneration (PLAN)—a type of neurodegeneration with brain iron accumulation (NBIA) often referred to as infantile neuroaxonal dystrophy when onset occurs in early childhood—and early-onset dystonia parkinsonism (DYT/PARK-*PLA2G6*) [78]. *PLA2G6* mutations that impair catalytic function, leading to accumulation of phospholipids, is associated with PLAN; mutations that modify substrate preference or regulatory mechanisms lead to DYT/PARK-*PLA2G6* [79].

Early development is usually normal. Onset prior to age 21 years is seen in approximately 25% of cases; the rest presents before age 40 years [80–90]. Patients present with various symptoms, such as motor slowness [80,91], foot dragging [84,87,89], rest tremor [86,90], imbalance [91], psychiatric symptoms (depression or psychosis) [88,92], and cognitive decline [84]. Although the overall course is progressive [23], most patients initially respond well to levodopa but develop early levodopa-induced dyskinesias and motor fluctuations [80,89].

Imaging in DYT/PARK-*PLA2G6* demonstrates cerebral atrophy without iron accumulation and with evidence of presynaptic, nigrostriatal dopaminergic dysfunction in most reports [81,88,89,91–93]. *PLA2G6* (any phenotype) cases seen at autopsy have exhibited widespread LB pathology, SNpc and LC neuronal loss, and tau pathology [16]. Brain iron accumulation has been reported in some autopsy cases of *PLA2G6*, although in none with JP.

2.1.2.3. PARK-FBXO7 (PARK15). *FBXO7* encodes F-box only protein 7 which is involved in mitochondrial homeostasis along with parkin and PINK1 [94]. PARK-*FBXO7* is characterized by parkinsonism and upper motor neuron signs with onset generally at age 10–20 years [95–97]. There is a marked phenomenological heterogeneity with presentations ranging from predominantly spastic paraplegia [97], mixed parkinsonism/upper motor neuron symptoms [95], to relatively pure parkinsonism [96]. Other reported symptoms include cognitive impairment, dystonia, equinovarus deformity, supranuclear gaze palsy, oculogyric crises, chorea, tics, speech changes, dysphagia, and bowel/bladder incontinence [96,98]. Parkinsonism is levodopa-responsive; however, treatment is complicated by early-onset motor fluctuations, dyskinesias, and behavioral disturbances (psychosis) in most patients [95,96].

MRI brain is normal or shows generalized atrophy but functional imaging reveals significant striatal, presynaptic, dopaminergic dysfunction [95,96].

2.1.2.4. PARK-DNAJC6 (PARK19). *DNAJC6* (DnaJ heat shock protein family (Hsp40) member C6) encodes auxillin, a protein involved with clathrin-mediated endocytosis [99]. PARK-*DNAJC6* is characterized by two major phenotypes, determined by the nature of the genetic mutation. Patients with missense mutations or mutations that affect splicing and lead to reduced production of auxillin present at 7–42 years with isolated parkinsonism [100,101]. The rate of progression is often slow with symptoms evolving over several years [101], however rapidly progressive cases with early development of debilitating symptoms have also been described [100]. On the other hand, patients with nonsense mutations resulting in a truncated protein product present at age 10–11 with parkinsonism in combination with intellectual disability, cognitive decline, upper motor neuron signs, dystonia, and epilepsy [102,103]. These patients were non-ambulatory within 10–15 years after onset [102]. Most patients with PARK-*DNAJC6* respond well to levodopa, however dyskinesias and behavioral symptoms often adversely impact their quality of life.

MRI is unremarkable [100,101], although a single case was reported

to have generalized cerebral atrophy [102]. Functional imaging revealed presynaptic, striatal, dopaminergic denervation [101].

2.1.2.5. PARK-SYNJ1 (PARK20). *SYNJ1* encodes synaptojanin 1, a polyphosphoinositide phosphatase which plays an important role in synaptic vesicle dynamics [104]. Although JP has been described [105,106], many patients with *PARK-SYNJ1* have onset of relentlessly progressive parkinsonism in their 20's and 30's [107–109]. Some patients also have dystonia, dysautonomia, eye movement abnormalities, and cognitive decline [106,109,110]. Early development is generally normal, but most patients experience generalized seizures in infancy [105–107].

Response to levodopa is variable [32] and any beneficial response is typically limited by emergence of side effects at low doses [106,110]. However, an excellent response to levodopa without complications has also been described [105]. MRI is normal or shows generalized atrophy and functional imaging reveals severe, bilateral, nigrostriatal dopaminergic deficit [107].

2.1.2.6. PODXL. *PODXL* encodes podocalyxin-like protein which is involved with neural development and formation of synapses [111]. Mutation in the *PODXL* gene has been reported to be associated with JP in 3 members (age at onset 13–17 years) of a consanguineous Indian family [112]. Patients appeared to have typical levodopa-responsive parkinsonism. However, all had moderate to severe rigidity, dystonia (either while on or off levodopa), and were dependent on assistance for activities of daily living at the time of evaluation 4–5 years after onset, suggestive of rapid progression. Presence of bradykinesia and normal MMSE was reported in one patient; the others were reported to be unable to perform these tests for unclear reasons. MRI brain was normal. *PODXL* awaits confirmation as a JP gene in other families.

2.1.2.7. PTRHD1. In 2016, Jaberi and colleagues described two brothers, born to consanguineous parents, who exhibited intellectual decline in childhood following a period of normal development; in their 20s, the phenotype evolved into progressive asymmetric parkinsonism (bradykinesia, rest tremor, postural instability, gait disturbance, freezing of gait), dysarthria, lower limb muscular atrophy, hyperactive deep tendon reflexes, and extensor plantar responses [113]. Both responded well to levodopa, although one experienced levodopa-induced dyskinesias after 2 years. The brothers harbored mutations in two genes: *PTRHD1*, encoding peptidyl-tRNA hydrolase domain-containing 1, and *ADORA1*, encoding adenosine A1 receptor, of which the latter was thought to be causative. Two other groups have since described a similar phenotype in patients with *PTRHD1* mutations [114,115], suggesting that *PTRHD1* mutations were also causative in the original report by Jaberi and colleagues. Patients with *PTRHD1* mutations may further exhibit psychiatric problems (anxiety, hypersexuality), cognitive impairment, hypersomnolence, and saccadic ocular pursuit. Out of a total of 7 reported patients, only 1 was thought to have JP while the remaining had onset of parkinsonism in their 20's [115].

2.1.2.8. PARK-VPS13C (PARK23). Vacuolar protein sorting 13 C (VPS13C) is involved mitochondrial activity and vesicular trafficking [116]. Mutations in *VPS13C* have recently been described as a cause of early-onset, atypical parkinsonism with initial levodopa-responsiveness, rapid progression, early cognitive dysfunction, and upper motor neuron signs. Only a single juvenile case has been reported [117].

2.1.3. Autosomal dominant juvenile Parkinson's disease

2.1.3.1. PARK-SNCA (PARK1, PARK4). The most common types of autosomal dominant PD, *PARK-LRRK2* (PARK8), *PARK-SNCA*, and *PARK-VPS35* (PARK17), are clinically indistinguishable from iPD [118]. PARK-*SNCA* (alpha synuclein) causes adult-onset PD but has been associated with juvenile onset in 0.7% of cases. Patients with PARK-SNCA may have a higher rate of non-motor symptoms, atypical clinical signs, and cognitive decline (65%, 83%, and 70%, respectively) compared to *PARK-LRRK2* and *PARK-VPS35* [118]. The clinical phenotype of PARK-*SNCA* is heterozygous although higher gene dosage (copy number) correlates with earlier age at onset and faster progression of motor and cognitive symptoms [119]. Pathology is characterized by LB and neuron loss in the SNpc, LC, and possibly other brain structures [16]. Hippocampal and cortical involvement is often prominent, which may help explain the relatively high frequency of cognitive decline in PARK-*SNCA*.

2.1.3.2. 22q11.2 deletion syndrome. Formerly known as DiGeorge syndrome, 22q11.2 deletion syndrome (22q11.2DS) has emerged as a genetic PD risk factor, accounting for 0.5% of patients with EOPD (mean age at onset, range: 40 years, 18–58), although 71.4% of patients with the deletion present with EOPD [120]. 22q11.2DS-related PD is largely indistinguishable from iPD; pre-existing motor symptoms (dysphagia, dysphonia, postural instability, impaired manual dexterity), non-motor symptoms (hyposmia, fatigue, constipation), and other conditions in childhood (hypernasal speech, congenital heart defect, recurrent infections, hypocalcemia, hearing loss, hypothyroidism) which are present in some patients may be distinguishing features. Levodopa-response, imaging, and pathology in 22q11.2DS-related PD is similar to iPD [120,121].

2.1.4. Other monogenic disorders

2.1.4.1. DYT/PARK-GCH1 (DYT5a; dopa-responsive dystonia). *GCH1* encodes GTP cyclohydrolase 1, the rate-limiting enzyme in tetrahydrobiopterin (BH4) synthesis. BH4 is an essential cofactor for tryptophan hydroxylase and phenylalanine hydroxylase and therefore required for synthesis of dopamine and other monoamines [122]. *GCH1* mutations lead to autosomal dominant DRD. This disorder is classically characterized by childhood-onset dystonia (mean age at onset, range: 8.5 years, 0–48) [123] with diurnal variation and improvement with sleep in most but not all patients [122]. The phenotypic expression is broad and ranges from isolated focal limb dystonia, generalized dystonia, or parkinsonism to a cerebral-palsy like syndrome with mixed movement disorders [122]. Many patients exhibit parkinsonism, particularly at the end of the day or when under stress which can lead to the diagnosis of JP. The phenotypic heterogeneity may lead to misdiagnosis as cerebral palsy, particularly when upper motor neuron signs are prominent [124,125], or epilepsy, hereditary spastic paraplegia, a neurodegenerative disorder etc. [126]. However, misdiagnosis has also been reported in straightforward cases [127]. An excellent response to even low doses of levodopa (e.g., 300 mg/day) is typical and long-term complications (dyskinesias and motor fluctuations) are rare in comparison with PD [122,128]. All children with dystonia should therefore undergo a “levodopa challenge” [122], even though some have challenged this practice [129].

Functional imaging of presynaptic dopaminergic neurons in the striatum reveal normal or only mild dysfunction in DRD compared to PD [130,131]. DRD is not associated with neurodegeneration [132,133]. Interestingly, *GCH1* variants may be associated with an increased risk of PD in relatives of patients with DRD [134].

DRD can be diagnosed based on history, examination, and significant improvement with relatively low doses of levodopa, coupled with genetic testing, normal functional neuroimaging, and/or positive phenylalanine loading test in some cases [135,136]. There is some controversy whether levodopa challenge is appropriate to support the diagnosis of DRD, but this may be the most effective and efficient way to make the diagnosis [129,137].

Autosomal recessive *GCH1*-related DRD has also been described, but is considered rare. Another cause of DRD is mutations of the gene for tyrosine hydroxylase (TH) which is inherited in an autosomal recessive fashion often with infantile onset [122].

2.1.4.2. DYT/PARK-ATP1A3 (DYT12; rapid-onset dystonia-parkinsonism). Mutations in *ATP1A3* (Na+/K + -ATPase subunit alpha 3) can lead to rapid-onset dystonia-parkinsonism with autosomal dominant inheritance and onset in the 2nd to 4th decade [138–140]. Patients presents with acute onset dystonia affecting the upper body and oro-bulbar region with predominantly axial parkinsonism, often triggered by physical or psychological stress. Dystonic symptoms frequently show a rostral-caudal progression. The symptoms are usually not responsive to levodopa (or DBS), but some benefit may be seem with benzodiazepines. Other phenotypic expressions of *ATP1A3* mutations include CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss) and hemiplegic migraine. MRI brain is generally normal, functional imaging does not show changes in striatal dopamine transporters [141], and neuropathology is notable for various changes including mild depigmentation and neuronal loss in the SNpc, but absence of LB [142].

2.1.4.3. DYT/PARK-TAF1 (DYT3; "Lubag"; X-linked dystonia-parkinsonism). Another rare disorder with dystonia and parkinsonism is X-linked dystonia-parkinsonism (DYT3, "Lubag") due to mutations of *TAF1*, a subunit of transcription factor IID which is involved in gene transcription [143]. Although usually adult-onset (mean age at onset, range: 40 years, 12–64) and triphasic—progressing through a "dystonic phase", then "dystonia-parkinsonian phase", and then "parkinsonian phase"—parkinsonism with or without dystonia may be the initial symptom of *DYT/PARK-TAF1* in childhood [144].

2.1.4.4. DYT-ATP7B (Wilson's disease). WD is a disorder of copper metabolism with autosomal recessive mode of inheritance [145,146]. More than 700 mutations in *ATP7B,* which encodes transmembrane copper-transporting ATPase 2, has been associated with the disorder [146]. ATP7B serves two functions in hepatocytes: excretion of copper into bile and activation of ceruloplasmin by incorporation of 6 copper atoms into apoceruloplasmin followed by release into the systemic circulation.

The mean age at onset of neurologic WD is approximately 15–21 years, but onset from age 6–72 years has been reported [147]. The first clinical manifestation of WD is often either neurologic (18–68%) and/or hepatic (40–60%) [146]. The first neurologic sign is typically a movement disorder, of which dysarthria (58%) is most common, followed by dystonia (42%), gait problems (38%), tremor (36%), parkinsonism (17%), choreoathetosis (15%), and seizures (5%) (from Ref. [148]). Parkinsonism in WD is characterized chiefly by bradykinesia, rigidity, and postural instability. Rest tremor may also be seen but is rarely an isolated finding. Other types of tremor include postural ("wing-beating") and kinetic tremor. The most common sign in neurologic WD is dysarthria (85–97%) and other reported neurologic disorders include a fixed facial grimace ("risus sardonicus") due to facial dystonia, asterixis (negative myoclonus), chorea, cerebellar ataxia, epilepsy, and autonomic dysfunction. Upper motor neuron signs and epilepsy are atypical. Kayser-Fleischer rings are caused by copper deposition in Descemet's membrane resulting in brown or brown-green discoloration typically most evident in the superior and inferior corneal pole. Diagnosis of Kayser-Fleischer rings may be made by visual inspection, but slit-lamp examination if often required to confirm the diagnosis [149].

Typical MRI findings in WD include T2 hyperintense signals in the basal ganglia, thalami, cerebellum, midbrain, and pons [146]. These are the primary areas where pathological changes (cell loss, astrogliosis, and demyelination) are seen at autopsy. Global cerebral atrophy may also be evident on imaging and at autopsy. Brain MRI can be normal in some cases of neurologic WD [150]. Striatal, dopaminergic imaging is usually abnormal [151].

All patients with JP and juvenile dystonia should be screened for WD, including ophthalmological evaluation to rule out Kayser-Fleischer rings and routine laboratory tests including serum copper, serum ceruloplasmin, and 24-h urine copper. Liver biopsy could also be pursued if the combination of clinical evaluation and laboratory tests are equivocal. Genetic testing may have limited utility given the high number of potentially disease-causing mutations, although commercially available tests screen for the most common mutations. Absence of Kayser-Fleischer rings and normal neuroimaging is insufficient to rule out neurologic WD [150].

The primary treatment of WD consists of decoppering with the goals of restoring normalcy in the symptomatic patient or preventing symptom onset in the presymptomatic patient [152]. Trientene and D-penicillamine increase urinary copper excretion while zinc sulphate reduce copper uptake from the gastrointestinal tract. Symptomatic therapy with levodopa, anticholinergics, and botulinum toxin has been used with variable success. WTX101 (bis-choline tetrathiomolybdate), an oral first-in-class copper-protein-binding agent, is currently being evaluated in multiple centers [153].

2.1.4.5. CHOR-HTT (Huntington's disease). Huntington's disease (HD) is caused by a CAG repeat expansion within the *huntingtin* (*HTT*) gene [154]. CAG repeat length ≥40 is diagnostic for HD, but some individuals in the intermediate allele range (27–35 CAG repeats) may have motor, behavioral, and pathological features consistent with HD [155], usually occurring late in life. Juvenile HD—also known as the Westphal variant—accounts for approximately 5–10% of all HD cases [154]. In a large retrospective study of 580 HD patients, 69 had juvenile HD [156]. Compared to patients with adult-onset HD, juvenile HD was characterized by faster progression, higher disability, shorter disease course (early mortality), higher median CAG repeat length, and frequent onset with non-motor symptoms (cognitive decline, behavioral disturbance). Most juvenile patients had motor onset with parkinsonism, myoclonus, and dystonia, while chorea and ataxia were uncommon presenting symptoms. Epileptic seizures are present in 40% of patients with juvenile HD and helps to further distinguish this entity from adult-onset HD [157].

Classically, MRI shows atrophy of the caudate nucleus ("box car" lateral ventricles), putamen, and globus pallidus [158]. With progressive disease, global cerebral atrophy is invariably seen. Juvenile patients may also have cerebellar atrophy. Presynaptic, nigrostriatal imaging is abnormal in HD [159]. The neuropathology of HD is chiefly characterized by cell loss in the striatum, especially medium spiny neurons, followed by gliosis [160].

Since chorea is less common in juvenile HD, treatment with vesicular monoamine transporter 2 (VMAT2) inhibitors (FDA approved for chorea in adults with HD) is usually not indicated [161]. Treatment of motor and non-motor symptoms is otherwise symptomatic [154].

2.1.4.6. SCA-ATXN2, SCA-ATXN3 (spinocerebellar ataxia 2 and 3). Two other progressive, neurodegenerative, autosomal dominant, CAG trinucleotide expansion disorders that have been associated with JP are spinocerebellar ataxia (SCA) type 2 and type 3 (Machado-Joseph disease) [162–165] due to mutations in *ATXN2* and *ATXN3*, respectively. SCA2 and SCA3 show anticipation and age at onset is inversely proportional to CAG repeat length. Genetic testing is readily available.

The rate of SCA2 and SCA3 in familial parkinsonism series is approximately 0–8% [166], although SCA's represent a rare cause of parkinsonism overall. Other than parkinsonism, SCA2 is characterized by cerebellar ataxia, dysarthria, intentional tremor, hypotonia, ocular abnormalities (ophthalmoparesis, diplopia, saccadic eye movements, pseudoexophthalmus), psychiatric symptoms, and dysautonomia; SCA3 is characterized by cerebellar ataxia, ocular abnormalities (nystagmus, diplopia, pseudoexophthalmus), upper motor neuron signs, dystonia, and autonomic dysfunction [167]. Parkinsonism in SCA can be levodopa-responsive [8].

Typical MRI findings include pontocerebellar atrophy [168].

Presynaptic, dopaminergic, striatal imaging may be abnormal [169,170]. In parkinsonian patients with SCA2, some patients were reported to have SN neuron loss and presence of LB pathology [16], although these findings may be incidental. Pathological data for parkinsonian SCA3 patients is lacking.

2.1.4.7. CHOR-VPS13A (chorea acanthocytosis). The term neuroacanthocytosis refers to neurological disorders in which acanthocytes may be seen on peripheral blood smear [171]. Chorea acanthocytosis, the prototypical type of neuroacanthocytosis, is an autosomal recessive condition caused by mutations in *VPS13A* [171]. It is characterized by hyperkinetic movement disorders (predominantly chorea and orolingual dystonia), seizures, peripheral neuropathy, muscle atrophy, and hepatomegaly with onset in early adulthood. Parkinsonism has also been reported as the presenting symptom and may be seen in juvenile patients [172]. Other rare disorders with acanthocytes that can present with parkinsonism include McLeod syndrome, HD-like 2, and pantothenate kinase-associated neurodegeneration (PKAN; see below) [171].

2.1.4.8. Neurodegeneration with brain-iron accumulation. NBIA represents a group of rare, genetic, neurological disorders characterized by progressive brain iron accumulation, especially affecting the basal ganglia [78,173]. The mode of inheritance is autosomal recessive, except for neuroferritinopathy (autosomal dominant) and beta propeller protein-associated neurodegeneration (BPAN; X-linked dominant).

PKAN, the most common NBIA, is caused by *pantothenate kinase 2* (*PANK2*) mutations. The "classic variant" presents prior to age 6 years (90% of cases) [173] with gait changes, imbalance, upper motor neuron signs, and prominent dystonia (including tongue protrusion dystonia). Juvenile parkinsonism [174], chorea, Adie's pupil, and eye movement abnormalities may also be seen.

Mitochondrial membrane protein-associated neurodegeneration (MPAN) is caused by *C19orf12* mutations. The disorder begins in childhood or early adulthood and may be characterized by mixed upper and lower motor neuron signs (potentially leading to consideration of ALS) [175], optic atrophy, cognitive impairment, psychiatric/behavioral problems [176,177], dystonia, and parkinsonism. Rarely, patients with MPAN may present as JP with levodopa-responsive parkinsonism and levodopa-induced dyskinesia [178].

BPAN is caused by mutations in the *WDR45* gene and presents in infancy with delay of gross motor and language skills, intellectual disability, spastic paraplegia, hand stereotypies, and seizures followed by emergence of parkinsonism and/or dystonia during the teenage years or early adulthood [78].

Coenzyme A synthase (COASY) protein-associated neurodegeneration (CoPAN) presents prior to age 10 years with spastic paraplegia, lower limb dystonia, cognitive impairment, and oromandibular dystonia [179–181]. Parkinsonism, axonal neuropathy, and obsessive-compulsive disorder usually also manifests after a few years.

Neuroferritinopathy is a disorder of iron homeostasis due to a mutation in the *FTL* gene and presents from age 10–50 years (mean, 40 years). The presenting symptom is often a movement disorder, of which the most common are chorea, (orofacial) dystonia, tremor, and parkinsonism [182].

2.1.4.9. Hereditary spastic paraplegias. HSP represent a diverse group of neurodegenerative disorders characterized by progressive spastic paraplegia which may be the sole finding in "isolated HSP". Conversely, "complex HSP" is characterized by a combination of spastic paraplegia, cognitive decline, peripheral neuropathy, retinopathy, deafness, and urogenital dysfunction depending on the specific subtype. A few patients with HSP (SPG11, *KIAA1840; SPG15, ZFYVE26)* and JP have been described. HSP can be levodopa-responsive, although benefits are frequently short-lived [183–186].

2.1.4.10. RAB39B. Mutations in *RAB39B*, encoding Ras-related protein Rab39B, is associated with a diverse group of phenotypes, including childhood-onset epilepsy, autism spectrum disorder, and macrocephaly [23]. The mode of inheritance is X-linked. Parkinsonism usually develops in mid-life (age 30–60) [55], although JP has been described [187], and can be levodopa-responsive.

2.2. Miscellaneous genetic disorders: inborn errors of metabolism, dopamine transporter deficiency, mitochondrial disorders, and neuronal intranuclear inclusion body disease

Other than WD, DRD, and the NBIAs, many other inborn errors of metabolism can cause JP as highlighted in several recent reviews [188–191]. Several lysosomal storage disorder have been associated with movement disorders, most commonly ataxia, isolated rest tremor, dystonia, and myoclonus [188]. While mutations in the *glucocerebrosidase* (*GBA*) gene represent an important risk factor in late-onset PD, JP has not been associated with *GBA* mutations. On the other hand, JP has been described in other lysosomal storage disorders, including Niemann-Pick type C [192], Tay-Sachs disease [188], juvenile neuronal ceroid lipofuscinosis [193], and Chediak-Higashi syndrome [194]. Other rare metabolic disorders with JP include disorders of cholesterol metabolism such as cerebrotendinous xanthomatosis [195], disorders of amino acid metabolism such as glutaric aciduria type 1 [196] and homocystinuria [197], and others.

SLC6A3 mutations typically lead to classic infantile dopamine transporter deficiency syndrome (DTDS) which is characterized by nonspecific symptoms (e.g. irritability and poor feeding) and a heterogenous movement disorder which may evolve to a parkinsonism-dystonia phenotype over the years [198]. Patient with higher levels of residual transporter activity may present during adolescence after a period of normal development with levodopa-responsive JP and dystonia. Clues to the diagnosis include abnormal CSF monoamine metabolites (ratio of homovanillic acid to 5-hydroxyindoleacetic acid > 4.0) and absent or severely reduced presynaptic dopamine transporter activity on appropriate neuroimaging.

Mitochondrial dysfunction plays an important role in idiopathic, toxic (e.g. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]), and monogenic PD (.e.g. *parkin* or *PINK* mutations), but several primary mitochondrial disorders have also been reported to cause parkinsonism [191,199]. Respiratory chain defects usually present at birth with profound symptoms such as growth retardation, lactic acidosis, and developmental delay, but a period of normal development followed by a complex neuropsychiatric syndrome, including JP, has also been described [200]. Mutations in polymerase gamma 1 (*POLG1*) gene, often associated with chronic progressive external ophthalmoplegia, is another mitochondrial disorder that may present as JP [201].

Neuronal intranuclear inclusion body disease (NIID) represents a heterogeneous, neurodegenerative disorder characterized pathologically by eosinophilic hyaline intranuclear inclusions with neuronal loss in central, autonomic, and peripheral neuronal cells and severe depigmentation of the substantia nigra [202]. This rare disorder was first described in 1968 by Lindenberg and colleagues [203] and while it is usually sporadic, familial cases have been reported [204,205]. The juvenile and adult types commonly present with personality changes, cognitive decline, parkinsonism, and dystonia [202,204,206–208]. The clinical course is relentlessly progressive and a combination of other neurologic symptoms are invariably seen: seizures, oculogyric crises, upper motor neuron signs, neuropathy, intestinal pseudo-obstruction, and other signs of autonomic dysfunction. Levodopa-responsive NIID has been reported, although motor fluctuations and dyskinesias are common. Death usually ensues around 10 years from disease onset. Premortem diagnosis is possible through rectal biopsy demonstrating the characteristic intranuclear inclusions.

2.3. Acquired juvenile parkinsonism

2.3.1. Drug-induced

Dopamine receptor blocking agents (DRBA), such as antipsychotics (e.g. haloperidol, olanzapine, aripiprazole) or antiemetics (e.g. metoclopramide), or dopamine depleters (e.g. tetrabenazine) are associated with drug-induced parkinsonism (DIP) in a dose-dependent fashion [209]. However, multiple non-dopaminergic drugs including calcium-channel blockers, some antiepileptics (e.g. valproic acid), and antidepressants have also been associated with DIP [209]. The use of antipsychotics in the US increased more than 4-fold in children and adolescents between 1993-1998 and 2005–2009 according to one study [210], likely fueled by the perceived "benign" side effect profile of "second" and "third" compared to "first" generation antipsychotics. However, both DIP and tardive parkinsonism, is seen in children at rates similar to adults treated with antipsychotics [211]. DIP is usually characterized by masked facies and symmetric parkinsonism (rest tremor, bradykinesia, rigidity, shuffling gait) with onset after a relevant medication exposure. The symptoms are expected to resolve completely within days to months after discontinuation of the offending agent in DIP; however, tardive parkinsonism or a genetic form of parkinsonism may be a consideration if parkinsonism persists more than 3 months after discontinuation of the drug. Imaging of the presynaptic, striatal dopaminergic system is normal in DIP and tardive parkinsonism but abnormal in levodopa-responsive genetic parkinsonism (Table 1).

2.3.2. Autoimmune and infectious diseases

Anti-N-methyl-D-aspartate receptor (NMDAR)-encephalitis affects children of all ages and is considered the most common type of autoimmune encephalitis [212]. The classical female predominance is mainly seen in adolescence and young adulthood (age 12–45 years) [213]. Pediatric anti-NMDAR-encephalitis is often postinfectious or idiopathic, although ovarian teratoma can be seen in up to 1/3 of teenage females and should be part of routine screening [214]. The presentation in children is typically subacute onset of behavioral and personality changes, cognitive problems, depressed level of consciousness, seizures, autonomic and sleep dysfunction, and a variety of hyperkinetic movement disorders, including stereotypies, dystonia, and myorhythimia [214,215]. Psychosis is more prominent in adults compared to children. In a cohort of 18 individuals with pediatric anti-NMDAR-encephalitis (mean age at onset 12.4 years), the presentation was characterized either by marked neurological (13/18) or psychiatric (5/18) symptoms [216]. Hyperkinetic movement disorders were common, although some patients aged 12–18 years had bradykinesia (7/11) or tremor (3/11) compared to none of the 7 cases who were younger than 12 years. NMDAR-encephalitis is diagnosed by detection of IgG against the NR1 subunit of the NMDAR in CSF or serum. MRI may demonstrate mesial temporal T2 hyperintensity and contrast enhancement on T1 sequences, and EEG is often abnormal [217].

Also known as Von Economo's disease, encephalitis lethargica (EL) is characterized by acute onset of neuropsychiatric symptoms, sleep disorders, bulbar dysfunction (ptosis, ophthalmoplegia), and dysautonomia with either an akinetic-rigid (parkinsonian) or hyperkinetic movement disorder in children and adolescents [213]. Although the disorder is probably autoimmune and responds to immunosuppression, "EL" likely represents nothing more than a diagnostic placeholder. Some previously reported hyperkinetic EL cases [218] were later found to have NMDAR encephalitis [219], while other patients who might previously have been classified as akinetic-rigid EL were found to have dopamine D2-receptor antibodies [220]. Yet other EL cases may fall on the spectrum of post-streptococcal disorders [221]. There is limited evidence for a direct link with the influenza virus [222].

Parkinsonism is the second most common movement disorder in patients with systemic lupus erythematosus (SLE) after chorea [212]. The etiology of parkinsonism in SLE is unclear; however, cerebrovascular [8] and antibody-mediated processes have been suspected [223]. Parkinsonism in pediatric patients with SLE is characterized predominantly by tremor, rigidity, and akinesia [224]. Most patients are female and exhibit a combination of constitutional symptoms, skin lesions, joint pain, upper motor neuron signs such as upgoing plantar reflexes and hyperreflexia, as well as cognitive and psychiatric symptoms. Some patients have abnormal neuroimaging, characterized by signal abnormalities in the basal ganglia. SLE can be diagnosed based on established criteria [225]. The prognosis is overall good and a positive response to levodopa and immune suppressing therapy is seen in most cases [224,226].

Other reports of infectious or post-infectious parkinsonism were associated with dengue [227,228], mycoplasma pneumoniae [229,230], and several viruses including Epstein-Barr virus [231,232], Western equine encephalitis virus, St Louis encephalitis virus, Japanese encephalitis virus, varicella zoster virus, and coxsackie virus [10,233,234]. JP has also been reported in subacute sclerosing panencephalitis (chronic infection and neurodegeneration due to measles virus) [235,236]. Infection with human immunodeficiency virus (HIV) should be a consideration in at-risk children and adolescents with JP, although HIV-related parkinsonism has so far only been reported in adults [237].

Post-vaccination JP has also been reported, following measles vaccination in a 5-year-old boy who developed basal ganglia lesions on MRI [238], and after H1N1 vaccination in a 17-year-old girl who had transient, marked decrease in dopamine transporter function [239]. Both responded to levodopa.

Appropriate diagnostic testing in suspected infectious or autoimmune encephalitic parkinsonism include MRI brain, EEG, blood and CSF evaluation for antimicrobial or autoimmune antibodies.

2.3.3. Structural and toxic causes

Intrinsic or extrinsic lesions that distort the anatomy or circuitry of the basal ganglia are other important causes of JP. Examples include cerebrovascular accidents (ischemic and hemorrhagic stroke), hypotension, hypoxemia, trauma, space occupying infections (tuberculomas, abscesses), mesencephalic tumors, extra-axial compressive tumors, pineal gland cyst, obstructive hydrocephalus (e.g. aqueductal stenosis), cranial radiotherapy, and central pontine myelinolysis [240–248]. However, interruption of striatal connections with other brain regions may also lead to JP, such as reported in a 17-year-old woman with gliomatosis cerebri [249].

Toxin-induced parkinsonism is an exceedingly rare cause of JP and only few reports have been published. However, poisoning with carbon monoxide, organophosphates, cyanide, MPTP, carbon disulfide, 3,4-methylenedioxymethamfetamine (MDMA), toluene, methanol, and n-hexane are some of the suggested potential causes of JP [8,10].

Diagnosis of structural or toxic JP is usually straightforward based on history (e.g. toxic exposure or history of cranial irradiation), physical examination, and MRI brain with contrast. Some cases may respond to levodopa.

3. Approach to and treatment of juvenile parkinsonism

Most patients with JP have a genetic or other identifiable cause, but no pathogenesis-targeted therapies that favorably modify disease progression have been developed, although clinical trials for *GBA* and *LRRK2* carriers are currently under way [250]. Fig. 1 provides a flowchart for the approach to and symptomatic treatment of JP. The first step in the evaluation of a patient with JP is to exclude acquired (secondary) and potentially treatable conditions, such as DIP or infection. All patients should also at a minimum be screened for WD with serum copper, serum ceruloplasmin, and 24-h urine copper, before genetic testing is conducted. Patients for whom there is a strong suspicion for a specific inherited disorder can go directly to specific genetic testing; as an example, an individual presenting with epilepsy and parkinsonism in childhood and a family history of chorea should be tested for HD, while

Table 1
Genetic disorders that may present as juvenile parkinsonism.

Designation-gene	Location	Clinical features[a]	Comments	Levodopa-response[b]	MRI	Striatal dopaminergic imaging[c]	Pathology
Autosomal recessive							
PARK-*Parkin*	6q26	Typical	Possible onset with dystonia	+ LID, MF	NL	ABNL	SNpc neuron loss, rare LB
PARK-*PINK1*	1p36.12	Typical		+ LID, MF	NL	ABNL	SNpc neuron loss, possible LB
PARK-*DJ1*	1p36.23	Typical		+ LID, MF	NL	ABNL	SNpc neuron loss, possible LB
PARK-*ATP13A2* (Kufor-Rakeb syndrome)	1p36.13	Atypical	Eye movement disorders, UMN, psychosis, dementia, facial-faucial-finger mini-myoclonus	+ LID, MF, hallucinations	NL (early) or atrophy	ABNL	UN
PARK-*TH* (dopa-responsive dystonia)	11p15.5	Atypical	Often infantile onset, broad phenotype including dystonia	+ LID	NL	NL	NL, +/− depigmentation SNpc
DYT/PARK-*PLA2G6*	22q13.1	Atypical	Depression, psychosis, dementia, UMN	+ LID, MF	NL or atrophy	ABNL	SNpc neuron loss, LB
PARK-*FBXO7*	22.q12.3	Atypical	UMN, dystonia, supranuclear gaze palsy	+ LID, MF, behavioral disturbance	NL or atrophy	ABNL	UN
PARK-*DNAJC6*	1p31.3	Typical or atypical	Isolated parkinsonism or parkinsonism with epilepsy, cognitive decline, dystonia, and UMN	+ LID, MF, behavioral disturbance	NL	ABNL	UN
PARK-*SYNJ1*	21q22.11	Atypical	Epilepsy in infancy, dystonia, cognitive decline, eye movement abnormalities	+/-LID	NL or atrophy	ABNL	UN
PODXL	7q32.3	Typical	Severe rigidity, rapid progression	+ LID	NL	UN	UN
DYT-*ATP7B* (Wilson disease)	13q14.3	Atypical	Progressive dysarthria, parkinsonism, and dystonia. Kayser-Fleischer rings. Stigmata of hepatic dysfunction.	+/−	T2 hyperintensity in BG, thalami, midbrain, and pons. Global atrophy.	ABNL	Cell loss, astrogliosis, and demyelination in BG, thalami, cerebellum, and brainstem
CHOR-*VPS13A* (chorea acanthocytosis)	9q21.2	Atypical	Chorea, dystonia, seizures, peripheral neuropathy	–	Caudate atrophy	ABNL (rare cases)	Neuronal loss and gliosis in BG (predominantly caudate)
NBIA/DYT-*PANK2* (PKAN)	20p13	Atypical	Upper motor neuron signs, dystonia, parkinsonism, chorea, eye movement abnormalities	–	"Eye of the tiger" sign (pallidal T2 hyperintensity surrounded by hypointensity)	ABNL (mild changes)	Pallidal iron accumulation and neuron loss
HSP/NBIA-*C19orf12* (MPAN)	19q12	Atypical	Upper motor neuron signs => lower motor neuron signs, optic atrophy, cognitive decline, psychiatric disturbance, dystonia, parkinsonism	+/−	SN and pallidal T2 hypointensity (hyperintense pallidal "streaking" may lead to misdiagnosis of "eye of the tiger"/ PKAN), cerebellar atrophy	ABNL	Pallidal and SN iron accumulation with neuron loss; widespread LB, LN
NBIA-*COASY* (CoPAN)	17q21.2	Atypical	Dystonic-spastic paraplegia, cognitive impairment, neuropathy, oromandibular dystonia	UN	Caudate/putaminal swelling and T2 hyperintensiy, later T2 hypointensity in the GP with central hyperintensity (similar to "eye of the tiger")	UN	UN
HSP-*KIAA1840* (SPG11), HSP-*ZFYVE26* (SPG15)	15q21.1, 14q42.1	Atypical	Spastic paraplegia, cognitive decline, peripheral neuropathy	+/−	Thinning of the corpus callosum, white matter hyperintensities (frontal horns; "ears of the lynx sign")	ABNL	Spinal (+/− brainstem) corticospinal tract degeneration
PRTHD1	2p23.3	Atypical	Cognitive decline, later onset of parkinsonism ± UMN	+	NL	ABNL	UN
PARK-*VPS13C* (PARK23)	15q22.2	Atypical	Rapidly progressive, UMN, dementia	+	NL or atrophy	UN	Diffuse LB
Autosomal dominant							
PARK-*SNCA*	4q22.1	Typical	Juvenile onset rare (< 1%), early dementia in some	+	NL or atrophy	ABNL	SNpc and LC neuron loss, LB, LN
22q11.2DS	22q11.2	Typical	History of seizures; neurodevelopmental disorders, dystonia, and psychiatric disorders may precede motor symptoms	+	NL	ABNL	SNpc and LC neuron loss, LB, LN

(*continued on next page*)

Table 1 (*continued*)

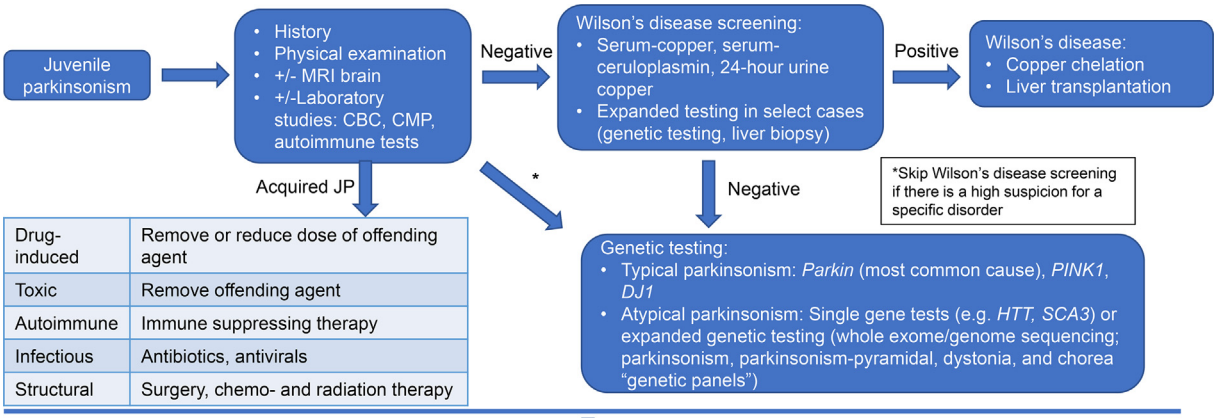
Designation-gene	Location	Clinical features[a]	Comments	Levodopa-response[b]	MRI	Striatal dopaminergic imaging[c]	Pathology
DYT/PARK-*GCH1* (dopa-responsive dystonia)	14q22.2	Atypical	Dystonia marked, broad phenotype, rare AR phenotype	+	NL	NL	NL, +/− depigmentation SNpc
DYT-*ATP1A3* (rapid-onset dystonia-parkinsonism)	19q13.2	Atypical	Orobulbar and upper body dystonia, axial parkinsonism, rostro-caudal progression	–	NL	NL	Broad spectrum of changes, including mild depigmentation and neuronal loss in SNpc, absence of LB
CHOR-*HTT* (Huntington's disease)	4q16.3	Atypical	Cognitive and behavioral disturbance; motor onset with parkinsonism and dystonia > chorea; seizures seen in 40%	+/-May worsen behavioral disturbance	Caudate and putamen atrophy, cerebellar atrophy often seen in juvenile patients, global cerebral atrophy	ABNL	Striatal (medium spiny neurons), pallidal, and cortical neurodegeneration, absence of LB
SCA-*ATXN2*, SCA-*ATXN3*	12q24.12, 14q32.12	Atypical	Ataxia and ocular symptoms, some cases may present with predominant parkinsonism	+/−	Pontocerebellar atrophy	ABNL	Pallidal, SNpc, and cerebellar neuron loss; LB (likely incidental)
NBIA/CHOR-*FTL* (Neuroferritinopathy)	19q13.33	Atypical	Chorea, dystonia, tremor, and parkinsonism. Low serum ferritin.	+/−	Cavitation/cystic changes in GP and putamen, T2 hypointensity with central hyperintensity in putamen, GP (mimicking "eye of the tiger"), thalamus, and dentate nucleus	NL	Cerebral and cerebellar atrophy, BG cavitation and accumulation of iron and ferritin
X-linked							
DYT-PARK-*TAF1* (X-linked dystonia-parkinsonism, "Lubag")	Xq13.1	Atypical	Triphasic with predominant dystonia at onset, parkinsonism may also be seen early	+/−	T2 hyperintense putaminal rim sign (all phases of disease), caudate and putaminal atrophy (combined dystonia-parkinsonism phase)	ABNL (may be normal in early disease)	Striatal neuron loss
NBIA/PARK-*WDR45* (BPAN)	Xp11.23	Atypical	Onset with mental retardation, spasticity, and seizures followed by parkinsonism and/or dystonia	+/-LID	SN > GP T2 hypointensity and T1 SN hyperintense "halo" (neuromelanin)	ABNL	Iron accumulation (GP, SN), tau neurofibrillary tangles diffusely
RAB39B	Xq28	Atypical	Epilepsy, cognitive impairment, macrocephaly	+/−	GP and SN T2 hypointensity CT: BG calcifications	ABNL	SNpc neuron loss, LB, and LN; abundance of cortical LB

ABNL = abnormal, BG = basal ganglia, GP = globus pallidus, LB = Lewy bodies, LID = levodopa-induced dyskinesias, LN = Lewy neurites, MF = motor fluctuations, NL = normal, SNpc = substantia nigra pars compacta, UMN = upper motor neuron signs, UN = unknown.

[a] Typical clinical features = bilateral (symmetric or asymmetric) parkinsonism (tremor, rigidity, bradykinesia). Atypical features = features atypical for Parkinson's disease, such as (but not limited to): rapid progression, early/severe dysautonomia, early cognitive decline, prominent psychiatric symptoms, prominent non-parkinsonian phenomenology (e.g. dystonia or upper motor neuron signs), and levodopa-unresponsiveness.

[b] Levodopa-response: "+" = significant improvement of parkinsonism, "+/−" = minimal or inconsistent improvement of parkinsonism, "-" = no improvement of parkinsonism.

[c] Position emission tomography (PET) using 6-[18F]fluoro-L-3,4-dihydroxyphenylalanine (F-DOPA) or single photon emission computed tomography (SPECT) using 123I-ioflupane (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (FP-CIT).



Symptomatic treatment

Symptom/sign	Primary treatment	Secondary treatment	Surgical
Parkinsonism	Levodopa, dopamine agonists	Dopamine agonists	STN or GPI DBS
Dyskinesia	Amantadine	-	STN or GPI DBS
Motor fluctuations	MAOI, COMTI, Levodopa ER	-	STN or GPI DBS
Dystonia	Botulinum toxin	Anticholinergics, benzodiazepines	STN or GPI DBS
Rest or re-emergent tremor	Levodopa, botulinum toxin, anticholinergics	-	STN or VIM DBS
Psychosis, behavioral problems	Quetiapine, clozapine	2nd or 3rd generation antipsychotic, mood stabilizer	-
Depression, anxiety	SSRI, SNRI, tricyclics, benzodiazpeines	-	-

Fig. 1. Evaluation and Treatment of Juvenile Parkinsonism.
CBC = complete blood count, CMP = comprehensive metabolic panel, COMTI = catechol-*O*-methyltransferase inhibitor, ER = extended release, GPI = globus pallidus interna, HTT = huntingtin, JP = juvenile parkinsonism, MAOI = monoamine oxidase inhibitor, PINK1 = PTEN-induced putative kinase 1, SCA3 = spinocerebellar ataxia type 3, SNRI = serotonin norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, STN = subthalamic nucleus, WD = Wilson's disease.

a patient with levodopa-responsive exercise-induced lower limb dystonia with an abnormal DaTscan should be tested primarily for mutations in *parkin, PINK1, or DJ1*. In most other cases, a higher yield may come from genetic "parkinsonism batteries" or more extended testing such as whole exome sequencing. All patients with troublesome symptoms should receive symptomatic treatment.

Patients with JP and juvenile dystonia should be tried on levodopa. Early emergence of levodopa-induced dyskinesias and motor fluctuations is common. In case of dose-limiting side effects, usual strategies employed for adults should be tried (Fig. 1) [251].

Dopamine agonists are preferred by some providers when treating PD, especially YOPD, in an effort to "delay" onset of levodopa-induced dyskinesias and motor fluctuations. However, dopamine agonists are less effective, are associated with lower quality of life, and do not truly delay onset of motor fluctuations and levodopa-induced dyskinesias compared to levodopa [252]. Further, in a longitudinal analysis of 306 adult PD patients without baseline impulse control disorders (ICD; hypersexuality, binge eating, compulsive shopping, pathological gambling), the 5-year cumulative incidence of ICD's was 51.5% in DA ever users compared to 12.4% in DA never users [253]. Although these results cannot be directly applied to a pediatric population, dopamine agonists should be used with caution in JP due to the potential for treatment over many years and thus a high cumulative risk of side effects.

Anticholinergics (trihexyphenidyl) are typically well-tolerated in the pediatric population compared to adults, but benefit is limited to dystonia and rest tremor. Common side effects include mouth dryness, eye dryness, urinary retention, and cognitive problems.

Botulinum toxin injections can be used for focal dystonia or in refractory hand tremor and is generally well-tolerated [254].

DRBAs with limited D2-receptor occupancy, such as quetiapine and clozapine, should be first line for treatment of psychosis as they are less likely to worsen parkinsonism compared to other drugs in that category [255]. The main limitation to use of clozapine is the (< 1%) risk of agranulocytosis [256]. Pimavanserin is FDA-approved for psychosis in PD, but has not been tested in the pediatric population [257]. Similarly, treatment of mood disorders, dysautonomia, and sleep disorders do not deviate from adults.

Deep brain stimulation (DBS) has been shown to be safe and effective in pediatric populations, especially in dystonia [258]. Canaz and colleagues reported a cohort of 11 children who underwent DBS at their institution, of which 2 JPD patients (one with *parkin* mutations) received bilateral subthalamic nucleus DBS [259]. Marked improvement of symptoms was noted as assessed by the Subjective Benefit Rating Scale and Hoehn and Yahr scale after surgery. In another report, 2 patients with JPD (one heterozygous for *PINK1* mutation) experienced limited benefit on parkinsonism based on validated rating scales [260]. Outcomes from DBS in monogenic or non-genetic YOPD is otherwise similar to outcomes in typical PD and these results can probably be extended to patients with typical JPD [261–263].

4. Conclusion

JP can be associated with marked morbidity and mortality. Although most cases have a genetic etiology, no pathogenesis-targeted, disease-modifying therapy has been developed. WD is an important exception in which early diagnosis can lead to effective treatment and prevention of disease progression. There has been an exponential increase in discoveries of new parkinsonism-related genes which has transformed our understanding of the phenomenology,

pathophysiology, genetics, and prognosis of different parkinsonian disorders. However, *parkin* mutations remains the most common cause of juvenile-onset levodopa-responsive parkinsonism that is otherwise indistinguishable from typical late-onset PD. Many disorders respond favorably to levodopa, but benefit is often offset by a higher frequency of levodopa-induced dyskinesias and motor fluctuations compared to late-onset PD. There is clear evidence that monogenic PD responds to DBS similar to idiopathic PD, and this observation may be extended to monogenic JPD but likely not to atypical JP.

Conflicts of interest

Nicki Niemann: None.

Joseph Jankovic:

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Author contributions

Nicki Niemann: Study conception, writing of the first and subsequent drafts.

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