Parkinsonism and Related Disorders 65 (2019) 39–48

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review article

Young-onset Parkinson's disease: Its unique features and their impact on quality of life

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ARTICLE INFO

Keywords:
Parkinson's disease
Young onset
Impact
Challenges
Management

ABSTRACT

Young-onset Parkinson's disease (YOPD), defined as age at onset between 21 and 40 years, presents unique motor and non-motor features that differentiate this subtype from the typical late onset Parkinson's disease (LOPD), starting after age 61. Because it affects patients in the prime of their life, it often has an extraordinary impact on their family, social, and professional life. While typically progressing at a slower rate than LOPD, patients with YOPD are more prone to develop levodopa-related motor complications, including dyskinesia. In this article we will review the clinical features and epidemiology of YOPD with focus on its impact on pregnancy, employment and family, as well as its particular diagnostic and management challenges.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by bradykinesia associated with either one or both of rest tremor and rigidity, as well a variety of non-motor symptoms [1–4]. Young onset PD (YOPD), also referred to as early-onset PD, has been somewhat arbitrarily defined as PD with onset of motor symptoms between ages 21–40 years [5], while onset at or before age 20 defines juvenile PD and onset after 60 defines late-onset PD (LOPD) [6,7]. However, consensus is lacking and the reported maximal age for YOPD has varied from 40 to 55 [6,8–10], while minimal age for late onset PD (LOPD) has varied from 50 to 70 [6,11,12]. In this review, we specified the age ranges whenever possible when referring to specific studies.

Because it affects people in the prime of their productivity, YOPD carries its own set of clinical, social, and occupational challenges. While increased genetic predisposition, slower progression, and increased risk of levodopa related complications are well recognized in YOPD compared to LOPD [8,13–21], in this review we will focus on more pragmatic aspects of YOPD, namely its impact on the patients' personal, professional and family life, and various management challenges.

1.1. Method: search strategies and selection criteria

A systematic review of available literature in Pubmed with the following search terms was performed: Young OR early AND Parkinson AND each of diagnosis, impact, management, challenge, pregnancy, employment, prevalence and family. All abstracts were reviewed for relevance to the topic of this review. Of the 1299 abstracts reviewed, 1066 were not considered relevant to the topic of this review as the search terms were vague to capture the most abstracts possible and minimize the risk of missing a relevant study; 133 abstracts were retained and the corresponding full articles were carefully reviewed. Of these, 71 full articles were considered relevant to the topic of this review and were included. Pubmed links and references from these articles were also scrutinized to identify other relevant studies as suggested by the references' titles. Similarly to the initial search, abstracts of potentially relevant references were reviewed, and, if considered relevant to the topic of this review, the corresponding full articles were reviewed. A total of 266 articles were reviewed.

1.2. Prevalence

The prevalence of PD in the western hemisphere has been reported to range from 130 to 200 per 100,000 in community based studies [22–25]. However, the prevalence and global burden related to PD is increasing at an exponential rate, largely due to rapidly aging population and improvement of life expectancy with a prevalence reported as high as 2000/100,000 in individuals over 80 years of age [22–25]. A review of 20 epidemiological studies from Asia reported a standardized all-age prevalence from 51 to 177 per 100,000 [26]. YOPD represents 5–7% of PD patients in the western hemisphere, but 10–14% in Japan [27]. It is unclear why YOPD would be relatively more frequent in

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https://doi.org/10.1016/j.parkreldis.2019.06.001
Received 14 January 2019; Received in revised form 29 April 2019; Accepted 1 June 2019

Japan, but the reported data is based on retrospective chart reviews and must be, therefore, interpreted cautiously [27].

1.3. Impact of YOPD

Young adults are more likely to be employed and have younger children and, therefore, the impact on overall productivity and prognosis is greater for YOPD than LOPD [28]. Because YOPD patients also have longer disease duration by the time they reach the age of the LOPD patients [29], they may suffer from more physical, economic, and psychological consequences. A number of cross-sectional studies have assessed the relationship between age at onset (AAO) of PD and quality of life (QOL) [6,30–34], the majority reporting an important association between younger onset and poor QOL [6,30–34]. This is likely due to a variety of factors including marital conflicts, difficulties with family life, social isolation and loss of occupation [28,34]. Greater worsening of QOL compared to the general population was seen in younger patients in one cross sectional study, attributed chiefly to physical limitations and role expectation [35].

Non-motor features of PD seem to have a particularly distressing impact on QOL of patients with YOPD. A cross sectional study of 426 PD patients and 402 controls reported that YOPD (AAO < 45) had a poorer QOL than LOPD (AAO > 45) and age matched controls, probably mediated to a large degree by a more depressive mood (OR 2.99 between YOPD and LOPD, $p < 0.01$, after adjustment for confounding factors) [33]. It is likely that social and psychosocial factors, including role expectations, contribute to greater impairment of QOL in young patients [34]. On the other hand, younger patients usually have a greater resilience because of stronger social support with younger and healthier spouse/care partner than older patients. Regarding longevity, a large retrospective US study found that the survival for PD patients was 32 years in YOPD (AA0≤49), 18.5 years in middle onset PD (MOPD)(AAO = 50–69), and 9.3 years in LOPD (AAO ≥70) [10]. In comparison, median survival in US males for similar age groups and around the same period was 47 years, 22 years and 9.5 years respectively with estimated loss of years of life of 15 in YOPD, 3.5 years in MOPD and less than a year in LOPD [10]. This and other studies confirm prior reports of a longer survival but greater loss of years of productive life with a younger AAO [36–38].

1.4. Genetics

It has been well recognized that the younger the AAO, the higher the risk of genetic predisposition [39]. Indeed, a family history of PD is reported in 20% of YOPD patients vs 6.9% of LOPD patients, and the age-specific risk of PD is 7.8-fold higher in the relatives of patients with YOPD compared to 2.9-fold among the relatives of patients with LOPD [10,15]. It is beyond the scope of this article to comprehensively review the genetics of PD, but we wish to highlight the most frequent causes of monogenetic forms of YOPD and their main clinical differences compared to apparent sporadic YOPD (Table 1).

PARK 1 (*SNCA,* 4q21-q23), appears to have a more rapid progression with early motor fluctuations compared to sporadic PD [40]. Furthermore, it is manifested by more severe psychiatric features, especially when caused by gene duplication [41–43]. On the other hand, PARK2 (*PRKN*, 6q26) has a slow rate of progression, but is frequently associated with some atypical features such as prominent involvement of legs, freezing of gait, dystonia, dysautonomia, sleep benefit, and marked levodopa sensitivity associated with motor fluctuations and dyskinesia [44]. While these patients have less cognitive impairment [45], impulse control disorders may be more severe [46]. PARK6 (*PINK1*, 1p36) also has a relatively slow rate of progression and the clinical features overlap with PARK2 [47,48]. PARK7 (*DJ-1*, 1p36) is also similar to PARK2 but may be more frequently associated with blepharospasm [49]. PARK 9 (*ATPA13A2*, 1p36), also known as Kufor-Rakeb syndrome, is frequently associated with spasticity, dementia, ophthalmoparesis as well as pallidal atrophy on brain imaging [50]. While homozygous GBA (1q21) mutations are known to cause Gaucher disease, heterozygous and occasional homozygous mutations in this gene have been found to markedly increase risk for PD, particularly in the Ashkenazi Jewish population [51,52]. These patients tend to have a

Table 1
Differential diagnosis of YOPD.

Genetic forms
PARK-*SNCA* (PARK1, 4q21-23)
PARK-*Parkin* (PARK2, 6q25.2–27)
PARK-*PINK1* (PARK6, 1p36)
PARK-*DJ-1* (PARK7, 1p36).
PARK-*LRRK2* (PARK8, 12q12),
PARK-*ATP13A2* (PARK9, 1p36)- Kufor-Rakeb syndrome
PARK-*PLA2G6* (PARK14, 22q13.1)- PLAN
PARK-*FBXO7* (PARK15, 22q12-q13)- early onset parkisonian-pyramidal disease
PARK-*VPS35* (PARK17, 12q11.2)
PARK- *DNAJC6* (PARK19, 1p31.3)
PARK-*SYNJ1* (PARK20, 21q22.11)
PARK-*VPS13C* (PARK23, 15q22.2)
DYT3 (TAF1, Xq13.1)- Lubag disease
DYT 5 (GCH1; 14q22.1-q22.2)- dopamine responsive dystonia
DYT 12 (ATP1A3, 19q13.2)- Rapid-onset dystonia parkinsonism
DYT16 (PRKRA, 2q31.2)- Young-onset dystonia parkinsonism
GBA,1q21- Gaucher's disease
Spinocerebellar ataxia 2 (ATXN2, 12q24)
Spinocerebellar ataxia 3 (ATXN3, 14q32.12)
22q11.2 deletion syndrome
Chediak-Higashi syndrome (LYST, 1q42.3)
Autosomal recessive hereditary spastic paraplegia (SPG-11; 15q21.1) and (SPG7,16q24.3)
Chorea-acanthocytosis (VPS13A, 9q21.2)
NBIA - PKAN (PANK2, 20p13)
MPAN (C19orf12, 19q12)- neurodegeneration with brain iron accumulation 4
BPAN (WDR45, Xp11.23)- beta-propeller protein-associated neurodegeneration
Huntington disease (Westphal variant) (HTT, 4p16.3)
Niemann-Pick type C (NPC1, 18q11.2 or NPC2, 14q24.3)
Frontotemptoral dementia and parkinsonism linked to chromosome 17 (MAPT, 17q21.31)
Cerebrotendinous xanthomatosis (CYP27A1, 2q35)
Dentatorubral pallidoluysian atrophy (ATN1, 12p13.31)
Juvenile neuronal ceroid lipofuscinosis (multiple genes and disorders)
Neuronal intranuclear (hyaline) inclusion body disease (NIID)
Mitochondrial diseases
Paraneoplastic
Anti-Ma2-paraneoplastic limbic encephalitis
Anti-N-methyl-D-aspartate receptor (*anti*-NMDAR) encephalitis
Central nervous system infections
Encephalitis lethargica
Japanese encephalitis
HIV/AIDS encephalitis
Mycoplasma
Neurosyphilis,
Prion diseases
Progressive multifocal leukoencephalopathy
Toxoplasmosis
Subacute sclerosing panencephalitis
Non-infectious potentially treatable
Wilson's disease
Drug-induced parkinsonism
Dopa-responsive dystonia
Structural lesion (vascular, tumoral, demyelinating)
Hydrocephalus
Hypoparathyroidism
Pseudohypoparathyroidism,
Chronic liver failure
Extrapontine myelinolysis
Systemic lupus erythematosus
Others
Carbon monoxide, cyanide, and methanol poisoning

Legend: YOPD: young onset Parkinson's disease, NBIA: Neurodegeneration with brain iron accumulation, HSP: hereditary spastic paraplegia, PKAN: Pantothenate kinase-associated neurodegeneration (formerly called Hallervorden-Spatz syndrome), NBIA: neurodegeneration with brain iron accumulmation

more rapid progression [53] and more severe cognitive impairment [54–58]. There is some heterogeneity between the different PD causing mutations on this gene, with severe mutations (including homozygotes or compound heterozygotes) having, compared to mild mutations, a higher PD risk (15 fold vs 3–4 fold) as well as earlier onset [59] and more severe motor and non-motor features [60].

1.5. Pregnancy

While there is no formal study on the impact of pregnancy on PD, a review of the literature reported worsening of PD-related symptoms in 31 out of 64 (48%) of pregnancies and improvement or status quo in 52% [61]. Of the pregnant women taking medications (83% of the total reported pregnancies), 36% worsened during pregnancy, compared to 67% of the untreated patients. This suggests that dopaminergic medications improve PD symptom during pregnancy and should be considered if the motor symptoms are troublesome. Among those who worsened (and for whom details of the PD therapeutic regimen was available), only 3 out of 9 pregnancies worsened because of a decrease in medication regimen motivated by the fear of teratogenicity and are detailed here. One patient was on rasagiline and pramipexole, both stopped [62], the second was on levodopa/carbidopa, entacapone, selegiline, and ropinirole, all of which were discontinued except for carbidopa/levodopa [63], while the third was on pramipexole which was stopped [64]. Parkinsonism worsened in 5 other pregnancies despite a stable or increased medication regimen, usually in the 2nd and 3rd trimester of pregnancy [65–69] while it worsened 1 month postpartum in 1 pregnancy despite an increase in medication doses during pregnancy [70]. No details were available regarding changes in the PD therapeutic regimen in the other 22 pregnancies [71,72]. A more recent series reported worsening in five of 14 pregnancies in PD patients. Parkinsonism worsened in one despite higher doses of levodopa, while the four others experienced transient worsening upon dose reduction that improved after subsequent dose increase: the first patient was only on pramipexole which was decreased during pregnancy, the second was on pramipexole which was decreased and rasagiline which was stopped, the third one was on benserazide/levodopa which was left unchanged and on amantadine and ropinirole both of which were discontinued, and the last patient was on a combination of pramipexole and rasagiline both of which were discontinued [73]. Overall, this suggests that worsening of parkinsonism is more likely a direct effect of the latter part of pregnancy, but can be exacerbated by medication reduction or withdrawal. The data is insufficient to suggest which agent's discontinuation is more likely to cause worsening. A common strategy seems to have been to continue levodopa if already used and discontinue other medications. Potential teratogenic effects of each agent should be taken into consideration as discussed below. In addition, pregnancy alters a woman's plasma volume, volume of distribution and metabolic state, leading to an alteration in drugs pharmacokinetics and a subsequent sub-therapeutic dosing of anti-parkinsonian medications. Thus, *anti*-PD medications must be frequently assessed during pregnancy and their dosage may need to be increased to prevent worsening of PD symptoms [74].

Many animal and human observations suggest that estrogen, particularly estradiol, has a protective as well as a dopaminergic effect in PD [18,61,75–84], while a smaller number suggests no benefit [75,85–87]. Other data suggest an increased risk of PD after exposure to exogenous estrogens [88,89]. During pregnancy, estrogen levels, particularly estriol, increase. Estriol has less affinity for estrogen receptors than estradiol [84,90] and, therefore, it probably plays a lesser role in modifying PD symptoms than the other hormones. Because of these inconsistent results, the role of estrogen and other female hormones in PD remains unclear. Some authors, however, observed that worsening of parkinsonism in the latter part of pregnancy in untreated PD patients could be secondary to a decrease in estrogens level at that period [63,67], and there have been anecdotal reports of worsening of PD symptoms just before and during menses [91].

Regarding the impact of PD on pregnancy, it does not seem that the disease impacts fertility, conception or the birth process in women with PD [75]. A literature review of 75 babies born to women with idiopathic PD reported only three fetal malformations (osteomalacia, ventral septal defect and inguinal hernia) [61]. However, all of these occurred in babies born to women who were taking anti-parkinsonian medications (namely carbidopa/levodopa, entacapone, selegiline, and benserazide/levodopa). After reviewing the anti-parkinsonian agents reported in each case and the outcome of pregnancy, the authors concluded that carbidopa/levodopa was the safest agent to use in pregnant women with PD, with no evidence of increased rate of teratogenicity, birth complications or miscarriages. Dopamine agonists were deemed possibly safe without evidence of any teratogenicity, though not recommended because of concern over 3 (8.6%) miscarriages and 1 (3%) placental abruption. Amantadine, however, showed teratogenicity and increased risk of miscarriages in many reports as well as animal studies and, should not be used during pregnancy [61,71,72,92]. There was insufficient data to make any recommendations regarding the safety of MAO inhibitors or COMT inhibitors during pregnancy [61]. In an additional series reporting on 14 pregnancies, dopamine agonists were used in 13 patients, levodopa/benserazide in 4, levodopa/carbidopa/entacapone in 1, rasagiline in 7, amantadine in 4, and biperiden in 1 patient, with a combination therapy used in 9 patients. Among these, 1 elderly mother gave birth to a child with Down syndrome, and one sibling from a twin pregnancy exposed to pramipexole and rasagiline died from unexplained liver failure. One woman had a miscarriage while on pramipexole, and there was neonatal distress when taking levodopa/benserazide, piribedil, and rasagiline which resolved spontaneously. No clear association between the medications and the outcomes could be established [73].

Dopamine inhibits the release of prolactin and, as such, levodopa and dopamine agonists reduce or inhibit lactation, although women have been reported to successfully breastfeed while on bromocriptine and carbidopa/levodopa [90,93,94]. However, data regarding the amount of medication excreted in breast milk and its impact on the infant are very limited, and breastfeeding while taking any anti-parkinsonian medications is not generally recommended [61,68].

1.6. Employment

Employment is another important issue for patients with YOPD and their families, not only because of financial implications due to disability-related loss of income and early retirement, but also because of the effect on social interaction and self-esteem. Indeed, a study comparing 75 YOPD (AAO < 50) and 66 LOPD patients (AAO ≥ 50) reported that, among those who retired, 97% of the YOPD retired early vs 73% of those with LOPD ($p = 0.003$) [34]. Other studies have found that 54% of YOPD patients retire early and 94% are likely to give up work within 10 years of disease onset [31].

Problems related to employment and long-term disability might be population specific. One retrospective cohort review of 88 Irish patients with PD onset before age 65 years reported that unemployment rates for males were 1.6 times higher compared to the general population, but unemployment among women was not significantly affected by PD [32]. Specifically, males aged 55–64 years were twice more likely to be unemployed than the general population. Median retirement age was 4 years earlier in PD patients compared to the general population. The authors also found that the median time to loss of employment was 7 years, with 40% still employed after 5 years from onset, and 14% after 10 years. Early age at PD onset and early diagnosis were associated with prolonged employment, consistent with the notion of slower progression of the disease in patients with earlier onset. These finding are consistent with other studies [8,95–97]. However, time from PD symptom onset to loss of employment was not influenced by gender, education status, type of work (manual, office, etc.), hours of work (full

time or part time), physical demands, use of hands or mental demands of the job. Among those who were still working at the time of the study, 77% had made adjustments at work, while 67% of those who had become unemployed or who had retired as a result of PD believed that adjustments such as changes in work schedule, type of work or having a longer time to complete tasks could have helped them to stay employed longer [32].

The challenge of staying employed with YOPD is not just related to the motor symptoms of PD. While physical disability is frequently cited as the greatest source of difficulty at work, many patients are most bothered by the perception that others might have of their impairment rather than by their impairment itself [32]. This higher level of stigma in YOPD patients [28]can manifest as a reluctance to seek help and ask for adjustments at work, which in turn decreases the chances of staying employed. While there are no formal studies assessing it, employers need to be educated about the work changes that could be beneficial to their employees with YOPD, such as the use of occupational therapy devices, reassignment to a desk job, or more lenient deadlines [32,66,97]. The importance of appropriate support in the workplace has already been well established [32,66,97]but does not seem to be sufficiently implemented. This requires employee's and employer's awareness and education about the patient's right to have reasonable adjustments made and what resources are available to do so. Finally, depression and addictive behaviors, more frequent in YOPD patients as we will detail below, likely contribute as well to employment related challenges [98].

Loss of earnings related to YOPD has been estimated to account for 65% of the total cost of the disease [32]; even those PD patients who continue to work earn markedly reduced incomes [99]. The burden of unemployment from YOPD goes beyond a financial cost, including social isolation, feelings of futility, lack of purpose, and lack of daily structure. In the study by Murphy et al. [32], 82% of those who had stopped working as a result of PD were dissatisfied with their unemployment status.

Patients with YOPD are particularly likely to face financial challenges and economic strain because of decreased working capacity, loss of income due to decreased productivity at work and early retirement, and inability to advance in the workplace, as well as the cost of medications and treatment [100]. Many people with YOPD seek long-term disability because part time employment may not provide enough income. Unemployed YOPD patients without family support face a grim future as they can become marginalized members of society and forced into low cost housing or early nursing home placement [101].

In summary, YOPD patients carry a greater socioeconomic burden when compared with their older-onset counterparts [28,34,102]because of the adverse impact of the disease on their financial status which often contributes to marital conflicts, social isolation, mood disorder, sexual dysfunction, and other aspects of family life [23,28,34].

1.7. Family

While no formal, controlled study has assessed the impact of YOPD on the patient's marriage and family, different authors suggest that YOPD presents an additional challenge, as many YOPD patients are only recently married and may have young children. PD can also affect sexual life, with a particularly stronger impact in younger patients [103]. Depression can decrease libido which leads to sexual difficulties and can, in turn, contribute to or exacerbate underlying depression. In addition, bradykinesia and rigidity can interfere with movements while sexual arousal can worsen levodopa induced dyskinesia [103]. When present, drooling can also decrease attractiveness. Erection can also be difficult to reach and/or maintain, and ejaculation can be either premature or delayed, the latter usually secondary to prescribed anti-depressants [103]. Marriages or relationships of shorter duration can be more vulnerable to the strain a chronic illness can impose than those of longer duration [104]. However, younger patients usually have younger and healthier spouse/partners who can provide more support. On the other hand, YOPD patients who have young children may be concerned and have a sense of guilt for not being able to fully devote themselves to them. Finally, the higher risk of burn out in caregiver of PD patients with ICD, depression and anxiety [105] and the higher frequency of these non-motor symptoms in YOPD (see below) raises the concern for a higher risk of burnout among YOPD caregiver, although this has not been formally demonstrated [105].

2. Clinical aspects

2.1. Diagnostic challenges

Although the clinical picture of YOPD usually resembles that of older-onset PD [8,29], the differential diagnosis is different [Table 1]. In a chart review of 337 patients, Rana et al. [9] found that YOPD (AAO < 45)patients had a much longer latency from onset to diagnosis (25 months vs 9 months,$p < 0.001$), and required more neurologist visits (3.64vs1.57,$p = 0.002$) and investigations (4.86vs0.36,$p < 0.001$) to receive the diagnosis. This observation underlines the challenge of making a diagnosis of PD in young individuals, despite a clinical presentation very similar to LOPD as neurologists suspecting PD seem to give preference to diagnoses other than PD in patients with symptoms presenting at young onset [9]. Indeed YOPD more likely than LOPD received a functional (psychogenic) diagnosis [106].

Another challenge could be a decreased acceptance of the diagnosis by younger patients. This can delay initiation of the appropriate therapy and further increased the negative impact of the disease on all aspects of the patient's life. Psychological counseling and support of the patient and the family should be provided in these circumstances.

2.2. Motor features

In a large retrospective study assessing the impact of AAO on clinical features and evolution of 593 patients, rigidity and painful cramps as the predominant initial symptoms were more frequent in YOPD (AAO ≤ 49) patients while gait instability as the predominant initial symptom was more frequent in older-onset patients [10]. While there was no statistically significant difference in the frequency of tremor or bradykinesia as the predominant initial symptom among the groups, tremor was the most frequent initial symptom in all groups with an overall frequency close to 62%, and the frequency increased with advancing AAO. These observations confirmed results of previous studies [107], while contrasting with others whose results indicated both an increased or decreased rate of tremor in younger onset patients [108–111]. Another review of 422 patients also reported that rigidity was a more frequent presenting symptom in the younger group (AAO < 50) [112]. In a study of 358 community-based and regional patients with PD, dystonia as a presenting symptoms was reported in 20% of YOPD (AAO < 45) but only 3% of LOPD (AAO > 64). Within 2 years of onset, dystonia developed in an additional 11% of YOPD and 1% of LOPD, suggesting that dystonia might be more frequent in YOPD [107]. Most studies agree that the YOPD patients tend to have a slower progression of motor symptoms than those with LOPD [7,38,113–116].

These clinical differences between YOPD and LOPD might have an anatomic substrate. In one study, Liu et al. [117]compared the striatal patterns of dopaminergic degeneration between YOPD(AAO ≤50)and LOPD(AAO > 50), as examined with [11C]-CFT PET. YOPD patient's DAT scans showed more sparing of the caudate compared with the putamen, while DAT scans from patients with LOPD showed relatively uniform involvement of both caudate and putamen. Since the caudate is more involved in psychomotor and complex cognitive functions [118–120], this might provide an explanation for the lower prevalence of these non-motor symptoms in YOPD compared to LOPD. On the other hand, a positron emission tomography (PET) and 18F-fluorodopa scans

study which included 27 patients reported a higher PD-induced increase in dopamine turnover compared with the decrease in dopamine synthesis and storage rate in patients of younger age compared with older patients. The authors suggested this implied greater alteration of dopamine turn over in YOPD that could lead to larger swings in synaptic dopamine levels, which has been suggested as a possible contributor to a greater risk of motor fluctuations [121]. In addition, a longitudinal PET assessment study reported a greater loss of putaminal dihydrotetrabenazine (DTBZ), reflecting a greater decrease in the density of the vesicular monoamine transporter type 2, in YOPD (average age 35) compared to LOPD (average age 70), with a slower progression and longer pre-symptomatic phase in the YOPD group. The authors concluded that YOPD patients progress more slowly and endure more damage to the dopaminergic system before motor symptoms develop, suggesting more efficient compensatory mechanism [122]. The higher risk of dyskinesia in YOPD patients could then also be attributed to a greater extent of neuronal loss in patients with similar severity of motor symptoms than their LOPD counterpart.

YOPD patients have less comorbidities, slower disease progression [38,113,123–125], less frequent gait disturbances as well as delayed falls and freezing [8,12], and delayed cognitive decline [29]compared to those with LOPD, and the lower frequency of non-dopamine responsive axial symptoms (dysphagia and postural instability) may be more dependent on AAO rather than disease duration even 20 years after onset [126]. On the other hand, some of the differences, e.g. cognitive decline, may be more dependent on absolute age rather than disease duration [29].

2.3. Response to dopaminergic therapies

Several studies have shown that YOPD is an independent risk factor for the development of levodopa-related motor fluctuations and dyskinesia [10,125,127]with a shorter latency from treatment onset in patients with YOPD compared to those with LOPD [5,8,128,129]. In two population based studies, the prevalence of dyskinesia was reported to decrease with advancing AAO; the 5-year risk was 50% with AAO before 50, 26% with AAO between 60 and 69, and 16% with AAO after 70 [130]. The authors suggested that the risk of dyskinesia was reduced by 20%–30% for each 10 years of older AAO [131]. To our knowledge, no data has been published reporting a difference in the nature or the severity of LID between YOPD and LOPD. While the use of levodopa is frequently reported as a risk factor for the development of motor fluctuations the notion of delaying levodopa therapy has been challenged [132,133]. In a cross-sectional case-control analysis of 91 patients in Ghana followed for at least 6 months after the initiation of levodopa therapy compared with 2282 Italian patients recruited during the same period, disease duration at the occurrence of motor fluctuations and dyskinesia was similar in the two populations even though levodopa therapy was introduced later in Ghana (mean disease duration 4.2 ± 2.8vs2.4 ± 2.1 years, $p < 0.001$) [134]. This suggests that delaying onset of levodopa therapy does not necessarily prevent levodopa-related complications [135]. Despite this evidence, a common practice is to avoid the use of levodopa as long as possible, especially in YOPD, and to consider alternatives such as dopamine agonists [8,136–139]. This “levodopa phobia”, however, often leads to inappropriately delayed effective treatment in individuals who need it the most, the otherwise productive patients with YOPD, with greater cumulative disability [135,140]. Furthermore, dopamine agonists can be associated with sudden sleep attacks [141], and other side effects, such as edema and impulse control disorder, which present an additional challenge to young patients who work, are looking after young children, or drive. YOPD patients are particularly prone to develop compulsive behaviors associated with dopamine agonists, such as hypersexuality, compulsive shopping and gambling and other features of impulse control disorder [142–144].

Therefore, the time and choice of *anti*-PD therapy must be individualized and tailored to the needs of the patient rather than AAO [145]. As such, levodopa should be started as soon as needed to reduce motor disability and its impact on professional and family life, with fewer potentially serious side effects than dopamine agonists. Once motor complications develop, their management is very similar in YOPD and LOPD, a discussion beyond the scope topic of this review [146–156].

Finally, a small European monocentric observational study (n = 54, average age 62 years) reported a lower drug compliance among younger patients, possibly related to a higher rate of depression [157], while a larger US population based study (n = 7593, 94% aged > 65 years) reported a decreased adherence with older age, possibly related to decreased income [158]. However, these findings were based on age at assessment rather than age at onset, and there is no data demonstrating any impact of AAO on medication compliance in PD.

2.4. Non motor features

YOPD patients are more likely than LOPD to face occupational and lifestyle challenges, not only because of motor impairment associated with their disease as noted above [8,28,159,160], but also because of emergence of relatively unique non-motor comorbidities, such as depression [159], loss of libido, sexual dysfunction, future uncertainty [163], and other problems [103]. In one study, depression occurred twice as frequently in patient with YOPD (AAO ≤ 49) as in patients with LOPD (AAO ≥ 70years) [10]. Although YOPD patients have a lower risk for dementia [164], several studies found that YOPD patients had a higher rate of depression and restless legs syndrome [8,12,34,102,125,126,165,166] as well as sexual dysfunction [167] than their older counterparts (Tables 2–4).

PD patients may be at higher risk for addictive behaviors [168], possibly because of the disease itself, but also as a side effect of dopaminergic medications used to treat the motor symptoms of PD. Impulse control disorders, such as gambling, compulsive shopping, and sexual addiction were reported with a nearly three-fold increase in those taking dopamine agonists (often a preferred class of *anti*-PD drugs in YOPD) and a 50% increase associated with levodopa treatment [169]. Dopamine dysregulation syndrome has been also associated with young AAO, especially in males [170].

In a cross sectional study of disabled Americans aged 30–54 years who were receiving Medicare, 57.7% of YOPD(AAO < 49)disabled cases were evaluated or treated for a psychiatric illness of any kind, and 40.7% of YOPD patients received care for depression in either the outpatient or inpatient setting, almost the double the frequency observed in the non-YOPD Medicare 30–54 year old beneficiaries for that year [171]. In addition, a diagnosis of, or treatment for, substance abuse or dependence was noted in 17% of YOPD patients, corresponding to a three-fold increase in the likelihood of these illnesses

Table 2
Findings that are less frequent, less severe or delayed in YOPD compared to LOPD [180 − 188].

Disease progression
Gait disturbances, including freezing of gait
Falls
Dementia
Anxiety
Psychosis
Double vision
Gastrointestinal complaints (constipation, gastroparesis)
Urinary complaints
Impairment of taste and smell
Daytime sleepiness
REM sleep behavior disorders
Insomnia
Nightmares

Legend: YOPD: young onset Parkinson's disease; LOPD: late onset Parkinson's disease.

Table 3
Findings that are more frequent or more severe in YOPD compared to LOPD.

Social stigma
Motor fluctuations
Levodopa-induced dyskinesia
Dopaminergic-induced impulse control disorder
Depression
Restless legs syndrome
Decreased quality of life
Loss in years of life
Familial/social difficulties
Sexual dysfunction

Legend: YOPD: young onset Parkinson's disease; LOPD: late onset Parkinson's disease.

Table 4
Findings that are more frequent or more severe in YOPD compared to age matched population.

Depression
Dysthymia
Generalized anxiety
Panic disorder
Social anxiety disorder
Acute adjustment disorder/psychosocial dysfunction
Impulsive compulsive disorders (gambling, shopping, and sexual addiction)*
Psychosis*
Substance abuse/dependence*
Dementia/mild cognitive impairment
Decreased life expectancy
Decreased quality of life
Early retirement/disability
Familial/social difficulties
Difficulty driving
Excessive daytime sleepiness

(* = from PD or treatment).
Legend: YOPD: young onset Parkinson's disease.

compared to the general disabled population. In that same cohort, substance abuse/dependence was the most frequently documented reason for hospitalization in YOPD, accounting for 82.6% of psychiatric hospitalizations, and 11.6% of all YOPD patient hospitalizations that year. YOPD patients also had a higher frequency of hospital admissions compared to non-YOPD disabled patients for impulse control disorders (fivefold increase), psychosis (threefold increase), acute adjustment disorder/psychosocial dysfunction (fourfold increase), and alcohol/substance abuse (twofold increase), without clear correlation to age, sex or race. Admissions for depressive and non-depressive psychiatric disorders were 1.4 fold more frequent in the YOPD disabled population [171]. That same cohort reported mild cognitive impairment and dementia in 19% of YOPD disabled patients, a 7-fold increase compared to same age non-YOPD disabled patients, with a steady increase in frequency with age. It is important to note that the denominator of these frequencies was the number of disabled, not total, YOPD patients. As such, the prevalence of cognitive decline, dementia, psychiatric illness, addiction and hospital admissions might be higher than in a working population of YOPD patients.

Additionally, because of difficulty with multi-tasking and processing, driving is frequently impaired in PD [172] and must be stopped at some point during the evolution of the disease. This can have particular implications for YOPD patients not only in terms of loss of independence, but also in relating to employment and self-esteem [6].

Finally, YOPD patients with poorly developed coping skills are at risk of exhibiting anger and self-destructive patterns of behavior [102]. They also seem to be more vulnerable to the lure of “miracle cures”, “media hype”, and unproven therapies such as supplements and stem cells [173]. The education of YOPD patients about their disease and providing adequate coping strategies and support system can become a challenge requiring a multidisciplinary team approach, consisting of social workers, physical and rehabilitation therapists and other allied health professionals [102,174–178]. In the specific case of YOPD patients, these health professionals can promote confidence and self-esteem, especially as related to their parenting and employment status [102]. Some patients with advanced YOPD may require counseling about accessing human resources and applying for disability despite their young age. Some authors advise that teenagers and young children be informed in a candid, but sensitive, manner about their parent's illness, be encouraged to take a responsible part in maintaining the family unity, and be part of decision making affecting the family [102]. These children may need professional counseling if their parent's illness is having a negative effect on their schooling and relationships.

There is a remarkable paucity of data based on prospective long-term studies that follow YOPD patients longitudinally until advanced age. Although cognitive decline seems to be a function of age rather than duration of the disease [179] and YOPD evolves slower than LOPD, the disease can still become devastating later in life. While we have focused on the differences between YOPD and LOPD, it is important to acknowledge that there is a marked variability in the expression and progression of the disease and that the two subtypes often overlap and may relate to other PD-subtypes [7,113–116].

3. Conclusion

YOPD presents unique challenges compared to LOPD as it typically affects patients in the prime of their life, impacting social, occupational, and familial dynamics, coupled with higher frequency of levodopa-related motor complications. Recognizing and addressing these challenges requires involvement of not only the patient and the treating physicians, but also the patient's spouse and children, as well as mental health providers, social workers, physical and rehabilitation therapists, and other health care professionals, with the goal of keeping the patients active and engaged in their family and to remain as productive as possible for as long as possible. We suggest that the primary role of the treating neurologist is to direct and help coordinate the care to maintain the most optimal quality of life.

Funding sources

None.

Conflict of interest/disclosures

Dr Mehanna serves as a consultant for Global Kinetic Corporation, and is on the speaker bureau for TEVA, Adamas Pharmaceuticals and Acorda Therapeuthics. He has received research grants form Lundbeck, Acorda and Solstice Neurosciences.

Dr. Jankovic has received research and/or training grants from: Adamas Pharmaceuticals, Inc; Biotie Therapies; Civitas/Acorda Therapeutics; Dystonia Coalition; F. Hoffmann-La Roche Ltd; Medtronic Neuromodulation; Michael J Fox Foundation for Parkinson Research; National Institutes of Health; Neurocrine Biosciences; NeuroDerm Ltd; Parkinson's Foundation; Nuvelution; Parkinson Study Group; Pfizer Inc; Prothena Biosciences Inc; Psyadon Pharmaceuticals, Inc; Revance Therapeutics, Inc; Sangamo BioSciences, Inc.; St. Jude Medical; Teva Pharmaceutical Industries Ltd.

Dr. Jankovic has served as a consultant or as an advisory committee member for: Adamas Pharmaceuticals, Inc; Allergan, Inc; Merz Pharmaceuticals; Pfizer Inc; Prothena Biosciences Inc; Revance Therapeutics, Inc; Teva Pharmaceutical Industries Ltd.

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