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An update on the management of young-onset Parkinson's disease

Nataša Klepac¹

Mario Habek¹

Ivan Adamec¹

Anabella Karla Barušić¹

Ivo Bach¹

Eduard Margetić²

Ivo Lušić³

¹Department of Neurology, Clinical University Hospital Zagreb, Medical School, University of Zagreb, Zagreb, Croatia; ²Department of Cardiology, Clinical University Hospital Zagreb, Medical School, University of Zagreb, Zagreb, Croatia; ³Department of Neurology, Clinical University Hospital, Medical School, University of Split, Split, Croatia

Abstract: In the text that follows, we review the main clinical features, genetic characteristics, and treatment options for Parkinson's disease (PD), considering the age at onset. The clinical variability between patients with PD points at the existence of subtypes of the disease. Identification of subtypes is important, since a focus on homogenous group may lead to tailored treatment strategies. One of the factors that determine variability of clinical features of PD is age of onset. Young-onset Parkinson's disease (YOPD) is defined as parkinsonism starting between the ages of 21 and 40. YOPD has a slower disease progression and a greater incidence and earlier appearance of levodopa-induced motor complications; namely, motor fluctuations and dyskinesias. Moreover, YOPD patients face a lifetime of a progressive disease with gradual worsening of quality of life and their expectations are different from those of their older counterparts. Knowing this, treatment plans and management of symptoms must be paid careful attention to in order to maintain an acceptable quality of life in YOPD patients.

Keywords: therapy, clinical features, dopamine agonist, levodopa, dyskinesia

Introduction

Young-onset Parkinson's disease (YOPD) is a subtype of Parkinson's disease (PD), occurring at a younger age, with specific symptoms, genetic correlation, and treatment strategies. YOPD is defined as the diagnosis of PD between the ages of 21 and 40.¹ A positive PD diagnosis under the age of 21 is referred to as "juvenile Parkinson's" (JP). Between 3% and 6% of all PD cases are reported to be YOPD.¹⁻³ Although most clinical features of JP and YOPD are the same, increased occurrence of dystonia and PD are found in families of patients with JP.⁴ The overall age and gender adjusted incidence of PD is 13.4 per 100,000, whereas the incidences for people between the ages of 30 and 39, 40 and 49, and 50 and 59 are 0.5, 2.5, and 9.8 per 100,000, respectively.⁵ Approximately 20% of YOPD patients have at least one first- or second-degree relative with PD either in the same or antecedent generation.⁶ The aim of this review is to give an overview of specific clinical manifestations, genetic background, and potential environmental factors of YOPD with strong focus on current treatment options and strategies available for YOPD.

Clinical manifestations

Although the diagnosis of YOPD is based on clinical symptoms and family history of Parkinson's disease or any other movement disorders, there must be exclusion of secondary causes of parkinsonian symptoms. Some of these secondary causes include Wilson's disease, dopa-responsive dystonia, drug-induced parkinsonism,

Correspondence: Nataša Klepac
Department of Neurology,
Clinical University Hospital Zagreb,
Medical School, University of Zagreb,
Kišpatičeva 12, Zagreb 10000, Croatia
Tel +385 9 854 1880
Fax +385 1 238 8784
Email natasa.klepac@zg.t-com.hr

spinocerebellar ataxia, iron accumulation disorders, and structural abnormalities. To exclude these possible secondary causes, such as drug-induced parkinsonism, a detailed history of all neuroleptic and antiemetic drug use should be recorded. Measurement of serum and urinary copper, and screening for Kayser–Fleischer rings should be performed to exclude Wilson’s disease.

Motor symptoms

The classical clinical appearance of PD consists of a resting tremor (3–6 Hz, usually unilateral on presentation), cogwheel rigidity, bradykinesia, and sometimes compromised postural reflexes and gait instability.^{7,8} Another sign, which is 100% sensitive but not completely specific for PD, may be a positive response to levodopa.⁷ The symptoms that appear in YOPD are similar to the classical symptoms of late-onset PD (LOPD), but some clinical features seem to be more prominent in YOPD.

In one study comparing clinical symptoms of YOPD versus LOPD it was concluded that YOPD patients more commonly present with increased muscle stiffness (43%), while LOPD patients more often present with increased difficulty walking later on in the illness (33%).⁹ Postural instability is more commonly seen in LOPD than in YOPD.¹

It was shown that “wearing-off,” “on–off” dystonia, and levodopa dyskinesia¹⁰ as well as dyskinesia in general¹¹ were much more prominent in YOPD patients (59% versus 37%).¹² Although, as previously mentioned, this very well could be a side effect of therapy.^{1,11,13,14} More specifically, it has been demonstrated that the most common type of dyskinesia is peak-dose dyskinesia, which includes stereotypic, choreic, or ballistic movements involving the head, trunk, limbs, and occasionally respiratory muscles.^{15–17} Another study confirming these findings showed that about one-third of YOPD patients had off-period dystonia, while LOPD patients were not observed to have dystonia during the study.⁹ The differences observed in the prevalence of tremor and bradykinesia between YOPD and LOPD were not statistically significant.¹⁰ YOPD patients were also shown to have increased motor fluctuations (69%) in comparison to LOPD patients (46%).¹² In JP dystonia (60% in JP versus 14% for YOPD) and akinetic rigidity (69% in JP versus 20% for YOPD) are much more common.¹⁸

Non-motor symptoms

It has been demonstrated that after median disease duration of 18 years, the prevalence of cognitive impairments is only 19%, of which 13% is under the age of 60.¹⁹ YOPD patients

have a decreased incidence of cognitive degeneration when compared with LOPD.^{1,18–20} It has been postulated that there may be a difference in the types of Parkinson’s between YOPD and LOPD with motor deterioration predominating the symptoms of YOPD and mental deterioration predominating the symptoms of LOPD.²¹

YOPD patients have been shown to have many psychological symptoms such as psychosis, confusion, and even hallucinations; these symptoms were present in only 13% of patients who had disease duration less than 10 years, and positively correlated with the duration of disease.¹⁸ Depression was also correlated with YOPD, this was postulated to possibly be a consequence of a longer duration of disease and decreased quality of life due to a high prevalence of motor symptoms.²² It was found that the mortality rate associated with YOPD is twice that of the normal population, but when compared with other PD patients it does not statistically vary.^{2,23,24}

Paresthesias were also found to be in 20.5% of YOPD patients compared with 2% of the LOPD patients.¹¹ Other non-motor symptoms, which were found to be more common in YOPD patients in comparison with LOPD patients, were restless legs and sweating.¹² The presence of symptoms in YOPD and LOPD is shown in Table 1.

Diagnosis

The diagnosis of YOPD is still widely based on the judgment of clinical symptoms. The recently US Food and Drug Administration (FDA)-approved DaTSCAN is being questioned for its accuracy and overall contribution to the diagnosis of PD. It has been shown that the overall accuracy of clinical diagnosis is 84% in early PD and 98% at later stages of PD. The diagnosis of PD clinically is mathematically just as accurate as the diagnostic accuracy of DaTSCAN imaging.²⁵ It must be kept in mind that the purpose of a

Table 1 Occurrence of symptoms in young- and late-onset Parkinson’s disease

Young-onset Parkinson’s disease	Late-onset Parkinson’s disease
<ul style="list-style-type: none"> • Motor fluctuations • “Off-time” dystonia • Muscle stiffness • Dyskinesia • Psychosis, confusion, hallucinations • Depression • Paresthesias • Restless legs • Sweating 	<ul style="list-style-type: none"> • Postural instability • Difficulty walking • Cognitive degeneration

DaTSCAN is to aid in the diagnosis of PD and not to be a replacement of the clinical diagnosis.

It has also been shown that transcranial ultrasound can show hyperechogenicity in the substantia nigra of a PD patient.^{26–28} It has been postulated that this is due to the increased concentration of iron in some patients with PD.^{26–29} Furthermore, lower serum ceruloplasmin levels have been correlated with a younger onset of PD.²⁶

Genetic background and potential environmental factors in YOPD

The genetic contribution to the etiology of YOPD is probably greater than in PD with later onset.³⁰ Out of several genes, assumed to be associated with YOPD, five stand out and are mentioned more frequently in current literature than others (Table 2).³¹ Mutations in the *PARK2* gene are the most common cause of autosomal recessive YOPD^{31–34} with an onset before age 40.³⁵ *PARK2* is an E3-type ubiquitin protein ligase involved in the proteosomal degradation of target proteins, including α -synuclein.³⁶ The accumulation of this protein results in neuronal death in substantia nigra and locus ceruleus.³⁶ The second most common cause of autosomal recessive YOPD is *PINK1* gene mutation. The discovery of *PINK1* involvement in PD was the first evidence that a kinase signaling pathway could be important in the pathogenesis of dopaminergic nigral cell death.³⁷ Moreover, it provided a link between mitochondrial dysfunction and neurodegeneration seen in PD.^{38,39} Another gene thought to be associated with YOPD is *PARK7*, involved in protection from oxidative stress

and chaperoning proteins such as α -synuclein.³⁶ PD associated with *LRRK2* mutations presents an onset distribution very similar to that seen in idiopathic PD, as well as clear age-dependent penetrance.^{40–42} In 2009, Tong et al demonstrated that *LRRK2* mutation affects activity-dependent dopamine (DA) neurotransmission and catecholamine release.⁴³ Lastly, mutations in *SNCA*, although rare, cause PD to occur at a younger age than that seen for idiopathic PD.⁴⁴ Given the correlation described recently between *LRRK2* and *SNCA*^{45,46} and the impact of α -synuclein overexpression on synaptic vesicle recycling,⁴⁷ the regulation of neurotransmitter release might arise as one of the main biological pathways compromised during neuropathology onset.⁴⁸ Additionally, a study conducted by Nichols et al suggests that patients carrying a glucocerebrosidase (*GBA*) variant exhibited PD symptoms 6.04 years earlier than those without a *GBA* variant.⁴⁹ It is also important to note that the abovementioned *LRRK2*, *SNCA*, and *GBA* gene mutations increase the risk of sporadic PD, whereas many others are linked to familial forms of PD.

Apart from genes, environmental factors may also play a role in YOPD etiology. A study from Sao Paulo by Aguiar et al observed higher exposure to well-water drinking in the YOPD patient group. Most of the patients were exposed during first or second decades of life, for an average period of 14.3 years.³⁴ Other potential environmental risk factors included pesticides, herbicides, and organic solvents. An inverse association between smoking and PD risk was not observed, suggesting a putative protective effect smoking might have on PD development. However, the authors argued that in the case of YOPD, the protective effects of smoking were not enough to overcome all other factors leading to neurodegeneration.

Table 2 Genes found to be significant in young-onset Parkinson's disease etiology and their mode of inheritance

Mode of inheritance		
Autosomal recessive	Gene product	Function
<i>PARK2</i> (OMIM*602544)	Parkin	Plays a role in the cell machinery that degrades unneeded proteins
<i>PINK1</i> (OMIM*608309)	PTEN induced putative kinase 1	Helps protect mitochondria from malfunctioning during period of cellular stress
<i>PARK 7</i> (OMIM*602533)	DJ-1 protein	Helps protect cells from oxidative stress
Autosomal dominant		
<i>LRRK2</i> (OMIM*609007)	Dardarin	Plays a role in activities that require interactions with other proteins, such as transmitting signals
<i>SNCA</i> (OMIM*163890)	α -synuclein	Plays a role in maintaining a supply of synaptic vesicles in presynaptic terminals

Current treatment options and strategies available for YOPD

Pharmacological treatment

Which drugs to use when initiating pharmacotherapy in YOPD is a complex treatment decision that depends on factors such as disease severity, functional disability, and psychosocial handicap, as well as individual aspects of comorbidity and age. To date, the most effective treatment for PD has been shown to be levodopa. It is effective in treating symptoms such as bradykinesia and rigidity. The effects of levodopa on postural stability, speech, and gait disturbance is less pronounced.

Initially, YOPD patients have a good response to levodopa therapy, but as treatment progresses, motor symptoms resistant to levodopa develop.^{6,13,21} It seems that YOPD patients

have a slower progression of disease but higher treatment complications with levodopa.^{1,11,13,14} In YOPD, treatment with levodopa is associated with early and prominent occurrence of motor complication, namely dyskinesia. In one study, it was observed that within the first week of treatment with levodopa, 25% of patients developed a complication; after 5 years of levodopa treatment, 91% of patients developed dyskinesias, and 92% developed motor fluctuations; and after 12 years, all patients had those side effects.²¹ A similar trend was demonstrated by a study done in 1987, where 100% of patients developed dyskinesias by the sixth year after therapy.⁶ Therefore, the treatment with levodopa should be postponed in this group of patients, although every PD patient progresses to the point where levodopa is necessary.⁵⁰

Alternative treatment options to start therapy in YOPD are dopamine agonists, inhibitors of monoamine oxidase B (selegiline hydrochloride, or rasagiline mesilate), amantadine hydrochloride, or where tremor is a particular problem, anticholinergics – although use of the latter might be restricted by cognitive side-effects.^{51,52} All of these drugs can be used alone or in combination with levodopa to successfully treat PD. The decisions as to when to start drug treatment and which drugs to use in patients with YOPD depend on several factors, including disease severity, functional disability, comorbidity, personal expectations, employment status, and psychosocial handicap.⁵⁰

Evidence suggests that the use of dopamine agonists rather than levodopa is associated with a decreased risk of developing motor complications.^{53–57} Long-term follow-up trials have confirmed that there are fewer dyskinesias and motor fluctuations in patients treated with dopamine agonists, but a decrease in moderate to severe dyskinesias was not noted to be very significant.^{58–60} This delay of dyskinesias and motor complications may be most appreciated in patients with YOPD.⁶¹ There is also some evidence that dopamine agonists may have a neuroprotective effect.⁶² This has been supported by functional imaging studies which demonstrate a decreased rate of decline of presynaptic dopaminergic functions.^{63,64} However, this conclusion comes from correlating the changes in imaging techniques rather than the clinical picture. Nonetheless, this information has led us to believe that starting therapy with dopamine agonists rather than levodopa could be beneficial. However, one must keep in mind that dopamine agonists also have many side effects. In PD patients treated with dopamine agonists, impulse control disorders including gambling, shopping, binge eating, and hypersexuality are observed. Other observed side effects of dopamine agonists are increased daytime sleepiness, leg

edemas, and early hallucinations.^{65–67} However, the method of treatment which has been most supported for YOPD is initiation of treatment with dopamine agonists, increasing the dose until a balanced level of effectiveness and the level of maximum tolerance is reached. Levodopa is then added as adjuvant therapy as needed.^{68,69} This method of therapy seems most suitable in YOPD for avoiding early motor symptoms due to levodopa treatment.

Monoamine oxidase (MAO)-B inhibitors are effective in monotherapy and as an adjunct to levodopa therapy, with beneficial effects on quality of life parameters in early and late stages of PD. Studies have shown that MAO-B inhibitors reduce the incidence of motor fluctuations, decrease the need for levodopa, and reducing overall disability, with negligible side effects. The MAO-B inhibitors, used as monotherapy, delay the need for the introduction of levodopa by about 9 months. These agents appear to be less efficacious than dopamine agonists but are better tolerated.⁷⁰

Amantadine could be used as a monotherapy or in combination with levodopa. There is some evidence that amantadine is useful in controlling dyskinesias, but evidence of its effectiveness in treating motor complications has not been convincing.^{71,72} Amantadine has been shown to reduce dyskinesia by 45% in patients with PD when it was compared with a placebo, but the positive effects were only sustained for 8 months, and when the patient experienced withdrawal from amantadine, there was an up to 20% increase in dyskinesias.⁷³ Therefore, amantadine is usually used as add-on therapy when dyskinesias develop.

Anticholinergics are nowadays rarely used due to side effects such as cognitive disturbances. Sometimes one may consider using anticholinergics for treatment of severe tremor in YOPD. The therapeutic approach differs in late and early phase of PD. In the late stage of PD in YOPD, motor complications such as wearing-off, unpredictable offs, and dyskinesias predominate. Therefore addition and manipulation of doses of levodopa, dopamine agonists, MAO-B inhibitors, and inhibitors of catechol-O-methyltransferase (COMT) can all be helpful in improving these complications. COMT inhibitors in combination with levodopa enhance efficacy of levodopa on motor symptoms of PD due to prolongation of its effect.

Despite all the therapeutic possibilities for treating YOPD, one must bear in mind that YOPD patients face a lifetime of a progressive disease and many years of therapy. When manipulations of oral antiparkinsonian drugs are exhausted, patients with YOPD may be good candidates for continuous apomorphine infusions, surgery, or continuous

levodopa treatment. For years it was believed that levodopa may have been toxic to dopaminergic neurons.^{74,75} Performance of levodopa infusions is a rather complex and expensive technique, which was a reason for restricting levodopa therapy for many years. Now opinions are changing, and it is believed that the decreased response to levodopa in late Parkinson's is due to progression of disease rather than toxic effects.⁷⁶ Moreover, it is thought that continued delivery of levodopa to the brain help to prevent and improve motor complications. Physiological continuous stimulation of the dopaminergic neurons has been explored through duodenal, intrajejunal, or subcutaneous infusions. It has been shown that continuous stimulations improve motor symptoms.⁷⁷

Surgery

Deep brain stimulation (DBS)

DBS is an FDA-approved surgical technique whereby electrical current is applied to various parts of the brain via implanted electrodes.⁷⁸ In contrast to ablative procedures, it proves to be a safer method in the treatment of movement disorders, producing adverse effects that are generally reversible once the stimulation is terminated.⁷⁹ The underlying mechanisms of DBS are not completely understood, although growing evidence supports the efficacy of DBS for the treatment of movement disorders including PD.⁷⁹

Over the years, many targets have been used for the treatment of PD, including ventral intermediate nucleus (VIM), subthalamic nucleus (STN), and globus pallidus interna (GPi).⁷⁹ Benabid et al found that in a series of 80 PD patients treated with either unilateral or bilateral VIM DBS, 88% had complete or near-complete tremor relief on the Fahn–Tolosa–Marin Tremor Rating Scale at 6 months to 8 years postoperatively.⁸⁰ The effects of VIM DBS on other symptoms of PD such as rigidity, bradykinesia, or drug-induced dyskinesia were either short lasting or nonexistent.⁸⁰ STN DBS does not improve on-medication state UPDRS motor subscores but does lead to 52% improvement in the off-medication state UPDRS scores over a period of 15 months postoperatively.⁸¹ A 50%–60% reduction in postoperative levodopa dose leads indirectly to improvement in levodopa-induced dyskinesia.^{81,82} On-medication dyskinesias are reduced by 94% after 12 months of STN DBS.⁸² Quality of life is significantly improved after STN DBS compared with medical therapy.^{78,83} However, recent data suggest that, although STN DBS improves motor components in both young and old patients, it is less effective in patients older than 65.⁸⁴ Nevertheless, a recent study by Odekerken et al suggests that STN could be the preferred target for DBS in patients with

advanced PD.⁸⁵ DBS-associated problems in cognitive, mood, and behavioral features seem to occur more often in the STN stimulation.^{85–89} In PD patients, GPi DBS improves tremor, rigidity, and bradykinesia in off-medication state as well as drug-induced bradykinesia, resulting in overall improvement in UPDRS motor scores.^{90–92} The most pronounced and long-lasting effect is the reduction in on-medication dyskinesia.⁹³ GPi DBS does not lead to reduction in the patient's levodopa requirement and might even increase after chronic GPi DBS therapy.⁹⁴ YOPD patients are usually characterized by a slower disease progression, lower incidence of non-levodopa responsive symptoms, and more severe motor complications,^{18,95–97} thus representing ideal candidates for the DBS surgical option.⁹⁸ A study by Merola et al showed that STN DBS-treated YOPD patients were associated with a medium- to long-term lower incidence of stimulation and medication resistant symptoms.⁹⁸

Ablation

Currently, the options for ablation therapy include pallidotomy or thalamotomy, where the target structure may either be the globus pallidus or the thalamus. Pallidotomy has been shown to reduce drug-induced dyskinesias and dystonias in PD patients who have previously had a successful response to pharmacological therapy.⁹⁹ A unilateral pallidotomy usually improves symptoms on the contralateral side.¹⁰⁰ There is a dispute whether a bilateral pallidotomy is a completely safe procedure.¹⁰¹

As with the pallidotomy a unilateral thalamotomy will be effective against symptoms on the contralateral side. It may improve tremor, rigidity, and dyskinesias but may worsen other parkinsonian symptoms such as bradykinesia, gait problems, postural instability, or speech disorders.^{74,102}

Currently there is a new noninvasive method which is emerging and has been approved by the FDA to enroll 30 patients in its study for ablation by transcranial magnetic resonance (MR) imaging-guided focused ultrasound.¹⁰² It uses focused ultrasound waves, which converge at a specific point determined and guided by MR to ablate the malfunctioning structure in the brain (nucleus ventralis intermedialis of the thalamus). The procedure includes real-time continuous MR imaging and MR thermometry monitoring, creating a very precise, safe, and effective way to treat patients.^{100,102–104}

Novel therapies

Emerging therapeutic options for treating idiopathic PD, such as neurotrophic factors, cell-based therapy, neurotransmitter targets, and potentially neuroprotective drugs, are

generating much interest but also controversy.^{105–108} Most recent treatment options for PD involve immunotherapy through vaccination and gene therapy. However, most of these treatment options focus very little on the YOPD subgroup of patients. Further research is needed to test their efficacy on YOPD patients specifically. These therapies are currently in experimental stages of development and have not been FDA approved.

Cell-based therapy

Cell-based therapy for PD has shown significant progress in recent years.¹⁰⁴ A major advancement came with the use of fetal ventral mesencephalic (VM) tissue as a cell source for transplantation. Fetal dopamine (DA) neurons transplanted into the striatum of PD patients have survived, integrated, and provided motor benefits.^{109–111} The first neural transplantation used dissociated fetal VM tissue, which was transplanted into the striatum of young PD patients. Marked motor improvement and increased fluorodopa uptake in the striatum on positron emission tomography (PET) was observed.¹⁰⁹ Indirect evidence of graft survival, obtained from PET studies, indicated that the transplanted fetal VM tissue can survive up to a decade and provide sustained motor benefits in PD.¹¹² Additionally, it was shown that DA neuronal suspension grafts can survive, integrate, and display mature VM phenotypes providing functional benefits in the degenerating brain for years without side effects such as dyskinesia.¹¹³ In a trial with solid pieces of fetal VM tissue, clinical improvement was, to some degree, observed in YOPD but not in non-YOPD patients.¹¹¹

Immunotherapy

PD, as the second most common neurodegenerative entity, is of particular interest with regard to applying immunotherapy in clinical practice.⁸⁸ The major component of Lewy bodies, and neuropathological hallmark of PD, is α -synuclein.⁸⁸ The first experimental indication that α -synuclein might be the causative agent in PD came from the analysis of rare autosomal dominant forms of PD in several families carrying three different point mutations in the SNCA gene leading to the formation of misfolded protein.⁸⁸ Masliah et al investigated mice overexpressing human SNCA and either administered a full-length α -synuclein-based vaccine employing CFA/IFA (Freund's complete/incomplete adjuvant) as adjuvant⁸⁹ or systemically administered an α -synuclein-specific monoclonal antibody.¹¹⁴ Both therapies were associated with reduced neurodegeneration and improved function. Recently, AFFITOPE[®] PD01 vaccine has been developed

to induce antibodies recognizing α -synuclein.⁸⁸ Preclinical studies involving the subcutaneous administration of the vaccine demonstrated reactivity towards α -synuclein with an additional functional benefit.⁸⁸ Compared with controls, PD01-treated animals showed superior cognitive functions as assessed by the Morris water maze test.⁸⁸

Gene therapy

In-vivo gene therapy is a new approach.¹¹⁵ Gene transfer of glutamic acid decarboxylase (GAD), rate-limiting enzyme in gamma-aminobutyric acid (GABA) production, and other methods that modulate the production of GABA in the subthalamic nucleus, improve basal ganglia function in parkinsonism in animal models.¹¹⁵ LeWitt et al assessed the effect of bilateral delivery of adeno-associated viral vector (AAV2)-GAD in the subthalamic nucleus compared with sham surgery in patients with advanced PD. The AAV2-GAD group showed significant improvement from baseline in unified PD rating scale (UPDRS) scores compared with sham group over the course of 6 months.¹¹⁵ A similar study involving neurturin, a naturally occurring analogue of glial cell-line-derived neurotrophic factor, was conducted by Marks et al¹¹⁶ by bilateral delivery of AAV2-neurturin into the putamen. However, it showed no motor score improvement using the UPDRS in treated patients after 12 months.¹¹⁶

The selection of the best candidate for surgery among PD patients is a debated topic. YOPD patients could be the best candidates for this kind of treatment, because they have a slower disease progression and more competent compensatory mechanisms, and this could be beneficial for effects of transplantations.¹¹⁷

Adjuvant therapies

Physical and occupational therapy in YOPD patients should be used with pharmacological treatment and may assist in the rehabilitation process. Initiating an exercise program from the earliest stages of PD might benefit secondary motor problems involving arm swing, gait, and posture.^{118,119} Exercise has been shown to improve physical function, health-related quality of life, leg strength, balance, and gait speed in PD, and is possibly mediated through increased calcium/CaM-dependent dopamine synthesis in the remaining dopaminergic nigrostriatal cells.^{120,121} Service (trained) dogs are reported to help people with PD by interruption of rest tremor on stroking the dog and diminishing propulsive gait,¹¹⁸ perhaps by providing visual cues.¹²² YOPD patients with speech difficulties might benefit from intensive voice therapy to maintain employment and social activity.¹¹⁵

Conclusion

Many clinicians view age at onset as an important determinant of clinical phenotype in PD. YOPD is very similar to LOPD in many ways but requires special attention because it is different enough to require a different treatment approach. The available evidence suggests that PD patients with younger age at onset have slower disease progression, an increased rate of dystonia at onset, a lower rate of dementia, and an increased rate of dyskinesias in response to levodopa treatment. Which drugs to use when initiating pharmacotherapy in YOPD is a complex treatment decision that depends on factors such as disease severity, functional disability, and psychosocial handicap, as well as individual aspects of comorbidity and age. Without clear proof of a drug's capacity to markedly alter or even stop the progression of the disease, there is no strategy that can be viewed as universal treatment. Dopamine replacement strategies offer greatest symptomatic relief and are needed whenever there is significant functional disability. Physicians are slowly gravitating towards the notion that levodopa treatment does not have toxic effects on dopaminergic neurons; however, preventing dyskinesias and motor symptoms which begin shortly after levodopa treatment initiation in YOPD patients remains to be demonstrated. The therapeutic strategy for YOPD patients should include a relatively low threshold for initiation of treatment. The treatment should be initiated with a dopamine receptor agonist, with the dosage individually adjusted. In the cases where the treatment response is suboptimal, or if problematic adverse effects develop, levodopa should be added to the therapy. YOPD patients are also ideal candidates for DBS therapy with medium- to long-term lower incidence of stimulation and medication resistant symptoms. Regular physical exercise and physical therapy must be encouraged. Emerging therapeutic options for the treatment of YOPD, such as cell-based therapy are generating much interest from the scientific community, although their effectiveness remains to be established. Future therapeutic strategies should focus not only on ameliorating the symptoms of PD, but also on neuroprotective or neurorescue therapies that can favorably modify the natural course of the disease and slow the progression of manifestations of PD. YOPD patients are not only bearing the burden of motor complications but psychological problems, often overlooked, and a general decrease in the quality of life. Many studies have shown that proper treatment can significantly increase the quality of life in YOPD patients. For this reason, a custom tailored treatment plan is of interest, based on stage of the disease, degree of interference of the symptoms with social and occupational functioning, and

response to treatment. The medical management of YOPD is complicated, and a multidisciplinary approach to care is vital to meet the psychological, emotional, and social needs of PD patients and their families.

Key points

- Diagnosis of PD before the age of 40 is considered YOPD.
- When suspecting YOPD, secondary causes of parkinsonian symptoms should be excluded (Wilson's disease, dopa-responsive dystonia, drug-induced parkinsonism, and structural abnormalities).
- After 6 years of levodopa therapy, almost all YOPD patients develop dyskinesias.
- Starting therapy with dopamine agonists delays the onset of levodopa-related motor symptoms until therapy with levodopa is initiated.
- DBS and ablation are available surgical options in the treatment of YOPD.
- Cell-based therapy, immunotherapy, and gene therapy are emerging therapeutic options in YOPD treatment.
- Physical and occupational therapy in YOPD patients should be used as an adjuvant therapy and may assist in the rehabilitation process.

Disclosure

The authors report no conflicts of interest in this work.

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