Treatment of young-onset Parkinson's disease: role of dopamine receptor agonists

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ABSTRACT

For mostly arbitrary reasons, the term “juvenile parkinsonism” is restricted to patients aged 20 years or younger, and “young-onset PD” (YOPD) is onset between ages 21 and 40 years. Previous studies suggest that YOPD has a slower disease progression and a greater incidence and earlier appearance of l-dopa-induced dyskinesias and motor fluctuations. Therefore, our therapeutic strategies have to respect the fact that YOPD patients face many years of gradual progression of disease and disability, a greater probability for developing various adverse effects of treatment, and worsening of quality of life. As an individually tailored treatment should be our primary goal, we must bear in mind that the needs and expectations of YOPD patients are different from those of their older counterparts. The therapeutic strategy for YOPD patients should include a relatively low threshold for initiation of treatment, and initiating treatment with a dopamine receptor agonist while maintaining an individually adjusted, moderately high threshold for switching to or adding L-dopa in cases where treatment response is suboptimal or if problematic adverse effects develop. It has been shown that some dopamine receptor agonists may also have antidepressive efficacy, thus potentially managing an additional problem associated with PD.

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1. Introduction

The age at onset of Parkinson's disease (PD) is a variable of uncertain significance. For mostly arbitrary reasons, the upper limit for early-onset parkinsonism is usually restricted to 40 years, although some studies include onset up to age 50–55 years [1]. After detailed analysis of their 60 cases with an early-onset of PD, Quinn et al. [2] restricted the term “juvenile parkinsonism” (JP) to patients aged 20 years or younger, and used “young-onset PD” (YOPD) for onset between the ages of 21 and 40 years. Several subsequent clinical, pathological and genetic studies support this arbitrary division. JP has proved to be rare, commonly familial, with atypical clinical features and pathology (e.g. most probably not caused by Lewy-body PD) [3]. In contrast to JP, most YOPD cases expressed a fairly pure parkinsonian syndrome due to typical Lewy-body PD or, less commonly, genetic causes [4]. Since patients in whom PD began between the ages of 21 and 40 years are the group in the most productive (both economically and socially) phase of their lives, consequences of pharmacological interventions in this population are of utmost importance [5].

2. Clinical characteristics of young-onset Parkinson's disease

The identification of monogenically inherited forms of PD [6] implies that PD is a heterogeneous group of diseases rather than just one entity. It has been assumed that heredity accounts for a greater proportion of YOPD cases than of older-onset cases [1]. Gasser [6] pointed out that, “as a rule, age at onset in many (but not all) of patients with monogenic forms of PD is younger than that of patients with sporadic disease”, although no other specific clinical symptoms or signs distinguished between these two groups of patients. Recently, Lohmann et al. [7] found no difference in the neurological, neuropsychological, and psychiatric features between early-onset PD patients with and without parkin mutation, except for significantly lower daily doses of dopaminergic treatment and greater delay in the development of l-dopa-induced fluctuations in parkin mutation carriers. Lewy body pathology is rare in patients with parkin mutations, which are present in approximately 9–20% of early-onset PD patients (in 6 of 104 YOPD patients in our series; 5.8%) [6]. On the other hand, a brain bank series showed no difference in the occurrence of Lewy body pathology between YOPD and older-onset PD patients [8]. Therefore, YOPD probably comprises a heterogeneous patient group, at least with respect to genetic aetiology, and may be different from older-onset PD. Enlarged hyperechogenicity of the substantia nigra on transcranial Doppler imaging is a much more common finding in older-onset than in YOPD patients [9]. With such a dilemma, the basic question is whether the term “YOPD” is still pertinent? Three studies used a data-driven cluster analysis as a statistical way to explore the presence of different clinical subgroups within...
PD and all identified the “young-onset” subgroup [10–12]. In addition, there is currently little direct evidence to support a pathophysiological difference between “non-genetic” YOPD and older-onset PD. Therefore, although in the majority of such cases YOPD has been considered as only the lower limit of the age range for presenting PD, previous studies suggest that YOPD has (a) a slower disease progression [13], (b) an increased rate of dystonia at onset of PD and during treatment [14], (c) a lower rate of dementia [4], (d) an increased rate of depression [15], and (e) an increased rate of l-dopa-induced motor complications [5].

3. l-dopa-related motor complications in patients with young-onset Parkinson’s disease

Some of the clinical characteristics of YOPD are of utmost importance for treatment decisions. As our primary goal should be individually tailored treatment, we must bear in mind that the needs and expectations of YOPD patients are different from those of their older counterparts [16]. They rated their quality of life (QoL) as worse in comparison to older-onset PD patients with a similar disease severity, at least in part due to specific social and psychosocial factors, including role expectations (e.g. marital, family, and socio-economic functioning) [17]. For instance, compared with older-onset PD patients, YOPD patients are more likely to be unemployed or have to retire earlier (on average, about 5 years after disease onset) [17]. Cessation of driving for them is not only significant in terms of stigmatization and loss of independence, but may directly influence professional activities and employment [18]. Compared with matched controls, YOPD patients have longer hospital stays, higher hospital costs and less independence upon discharge [19].

The available evidence suggests that YOPD patients have a slower disease progression. Jankovic et al. [20] found that YOPD patients reached the same level of disability as their late-onset counterparts (≥70 years) at a significantly slower rate (2.9 vs 1.7 years). The life expectancy estimate in patients with PD onset between 25 and 39 years was 38 years compared with 49 years in the general population, whereas in those with disease onset after the age of 64 years the equivalent estimate was only 5 years [21]. Therefore, our therapeutic strategies have to respect the fact that YOPD patients face many years of gradual progression of disease and disability, a greater probability for developing various treatment-related adverse effects, and worsening of QoL. Calne and Kumar [16] ironically stated that in this “long war” with the disease, “YOPD patients may outlive their physicians”.

These more benign features of YOPD are tempered by the observation that, after an excellent initial response to l-dopa, a younger age of onset is associated with a greater incidence and earlier appearance of l-dopa-induced dyskinesias (LID) and motor fluctuations [2,5,8,22]. LID in the parkinsonian population occur in approximately 30–40% of patients by 5 years of treatment [23] and in 59–100% of patients by 10 years [23,24]. Their appearance also predicts the onset of motor response fluctuations [25]. Grandas et al. [24] identified age at onset of PD and initial l-dopa dose as the main independent predictors of LID development. In another study [26], LID development was associated with an earlier age at onset and longer duration of PD, longer duration of l-dopa treatment, total exposure to l-dopa, female sex, and possibly genetic factors. Kumar et al. [27] also found that the risk of dyskinesia decreased with older age, with a 20–30% risk reduction for 10 years age difference. The 5-year LID incidence was 50% between the ages 40 and 59 years, 26% between 60 and 69 years, and only 16% in those aged 70 years or older [27]. However, for those with PD onset before the age of 40 years, estimates for this in several studies were higher than 90% [2,4,27], with similar figures for l-dopa-induced motor fluctuations [5]. In the study of Schrag et al. [4], more than 25% of the YOPD patients developed complications of l-dopa therapy within the first week of beginning treatment and more than 40% within 6 months. After 5 years, 91% and 92% of 99 YOPD patients had developed LID and motor response fluctuations, respectively.

The impact of LID on the QoL of PD patients is still controversial: some studies show significant impact or adverse effects on various dimensions of QoL, whereas others report no significant impact and suggest that LID may not pose a major concern for patients [1,28]. Most patients prefer mild-to-moderate dyskinesias to being “off” [28]. In a recent population-based study, LID at 10 years were rated severe enough to necessitate medication adjustment in 43% of patients, while they could not be medically controlled in only 12% [23]. Therefore, Encarnacion and Hauser [28] suggested that the effects of LID on QoL may depend on their severity, since “marked dyskinesias can cause functional impairment and patient discomfort”. Indeed, in their cohort of YOPD patients, Gómez Arevalo and colleagues [29] found that ballistic dyskinesias and severe dystonia, as well as biphasic dyskinesias, were significantly more frequent than in their older-onset counterparts. They also reported that YOPD patients were more significantly disabled by LID than those with older-onset PD. Increasing severity of LID is also associated with depression, poorer performance in activities of daily living, and an increase in healthcare costs [28]. Finally, Encarnacion and Hauser [28] pointed out that the expression of LID might limit the physician’s option to increase antiparkinsonian medication to reduce the “off” time.

Several hypotheses have been proposed to explain the greater incidence of l-dopa-induced motor complications in YOPD. One possible explanation is that the initial severity of nigrostriatal damage may differ with age of onset. Gibb and Lees [8] reported that the degree of nigral cell loss was greater in YOPD patients (by 24%) than in those with late-onset PD. In a recent PET study, Troiano et al. [30] demonstrated reduced dopamine transporter (DAT) expression in the putamen of PD patients with LID versus those without. Downregulation of DAT may compensate for decreased synaptic dopamine levels in early PD, but at the expense of leading to oscillating levels of dopamine, which may ultimately facilitate the development of LID [30]. However, several studies have demonstrated that the initial loss of nigrostriatal markers was not significantly different between YOPD and older-onset PD patients [31,32]. The only possible exemptions may be rare cases of autosomal-recessive parkinsonism associated with early-onset PD (PARK2, PARK6) [32]. Varrone et al. [33] found a more severe and a more symmetrical loss of striatal DAT density in PARK2 compared with non-PARK2 early-onset parkinsonism.

Although at an early stage of PD there are no significant differences in the severity of nigrostriatal damage in YOPD versus older-onset PD, de la Fuente-Fernández et al. [31] noticed that the subsequent changes, some of which are compensatory, may be age-dependent (e.g. loss of dopaminergic projections to the striatum, decline in striatal dopaminergic receptors, changes in dopamine turnover, as well as some extrastriatal changes such as loss of cortical neurons). Therefore, the authors suggested that “all these normal age-related changes, superimposed over the initial nigrostriatal lesion in PD, could very well cause initially identical nigrostriatal lesions to evolve differently in patients of different ages” [31]. Indeed, Sossi et al. [34] found that dopamine turnover in younger-onset PD patients underwent a relatively greater alteration and thus likely contributed to a greater imbalance between dopamine synthesis, storage and release, which could lead to larger swings in synaptic dopamine levels, thereby resulting in treatment-related motor complications.
The alternative hypothesis for the greater incidence of LID in YOPD is that they are a consequence of aberrant neuroplasticity in corticostriatal synapses caused by long-term non-physiological, pulsatile dopaminergic stimulation of striatal neurons [35,36]. Linazasoro [37] suggested therefore that LID could be regarded as maladaptive, negative consequences of neural plasticity, whose mechanisms might be under the control of age and genetics.

4. Initial treatment of young-onset Parkinson’s disease

It has been traditionally advocated to delay initiation of dopaminergic treatment in PD until symptoms progressed to a level of sufficient impact on patient’s professional and social functioning (“wait and watch” policy). This is particularly relevant for YOPD patients, since they progress more slowly and may not need treatment for some time [16]. However, such an approach has been challenged in several trials [38,39]. In contrast to the previous therapeutic attitude, it has been suggested that introducing medication at or shortly after the time of diagnosis may provide long-term benefit in terms of motor improvements and in delaying clinical progression, by preserving compensatory responses that maintain motor functions, limiting the effects of deleterious compensatory mechanisms, and by restoring the basal ganglia to a more normal physiological state [40]. In addition, some (but not all) recent studies have a shown rapid decline in QoL measures if symptomatic treatment is not initiated shortly after the diagnosis of PD [41].

Once the functional state of YOPD patients necessitates introduction of dopaminergic treatment, dopamine receptor agonists may be an optimal choice for this group of PD patients, considering the described tendency for earlier development of L-dopa-induced dyskinesia [42]. However, reports have shown rapid decline in QoL measures if symptomatic treatment is not initiated shortly after the diagnosis of PD [41].

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The described tendency for earlier development of L-dopa-induced dyskinesia (i.e. dyskinesia, wearing-off, “on–off” effects) were more common in the initial L-dopa group (68.4%) than in the initial pramipexole group (68.4%) as did initial L-dopa, with a longer time to the development of dyskinesia, a lower incidence of dyskinesia, but not of disabling ones, and a lower incidence of at least moderate wearing off. However, this study comprised only about one-fifth of the patients from the original cohort.

More recent reports from open-label long-term studies suggest that these differences tend to disappear as the disease progresses. In a 14-year follow-up of 166 surviving PD patients from an initial cohort of 782 (21%), Katzenschlager et al. [49] found that the rates and intensities of motor complications and dementia were not significantly different between the initial L-dopa group and the initial bromocriptine group, whereas disability and physical scores, as well as QoL, were better in the L-dopa group. There are no data favouring the potency of one dopamine receptor agonist over another in delaying the development of motor complications, and there is no reason to believe that another dopamine receptor agonist would provide better results than bromocriptine. Therefore, other factors besides the induction of motor complications during the first years of treatment need to be taken into account when choosing the initial therapeutic approach for a given patient (e.g. non-motor symptoms, consequences of long-term multisystem effects, etc.). This may be particularly important for YOPD patients who will possibly live as long as 25–30 years with the disease (and treatment) [16].

(b) Although in very early phases of PD dopamine receptor agonists provide antiparkinsonian benefit comparable to that initially provided with L-dopa, with disease progression their antiparkinsonian efficacy is considerably less than that of L-dopa [50]. In early PD, L-dopa improves total UPDRS score by approximately 5 points more than a dopamine receptor agonist, although QoL is not statistically different at 4 years [51]. Interestingly enough, exactly the same magnitude of difference (i.e. 5 points) was suggested to represent a clinically meaningful difference [52]. Some authors combine monoamine oxidase-B inhibitors with dopamine receptor agonist to hypothetically enhance efficacy and further delay the introduction of L-dopa [40]; a strategy that may be particularly relevant for YOPD.

(c) Virtually all, or at least the vast majority, of PD patients eventually need additional L-dopa to optimize control of the disease, usually within the first 3–5 years of the disease [40]. However, once L-dopa is added, motor complications accumulate at the same rate, regardless of whether L-dopa was used as an initial monotherapy or was added as a supplement to a dopamine receptor agonist, suggesting that the crucial role of dopamine receptor agonists in delaying motor complications is related to their ability to delay the need for L-dopa [50]. Considering the more benign course of the disease in YOPD, one may speculate that a possible period of initial monotherapy with dopamine receptor agonists prior to the necessity to introduce L-dopa may be longer in YOPD compared with older-onset PD patients.

(d) Dopamine receptor agonists have more potential adverse effects than L-dopa. Some of them (e.g. somnolence with excessive daytime sleepiness, postural hypotension) may be particularly important for YOPD since they may seriously interfere with professional activities (e.g. falling asleep at the wheel) [53]. Risk factors for a variety of impulse control disorders (ICDs) associated primarily with the use of dopamine receptor agonists (particularly at higher doses), such as pathological gambling, hypersexuality, binge eating, and compulsive shopping, may include – besides male gender – a pre-PD history of ICD symptoms (such as alcohol or substance dependence), a personality style characterized by impulsiveness, as well as younger age or younger age at PD onset [54]. However, Weintraub et al. [55] suggested that reports of younger PD
patients being disproportionately affected with ICDs may, at least in part, reflect prescribing patterns. Still, YOPD patients should be warned and followed for these problems. Newer once-daily formulations of dopamine receptor agonists, with steadier plasma levels and possibly fewer peak adverse effects, may be better tolerated [50].

5. Conclusion

Unfortunately, studies specifically devoted to establishing optimal therapeutic approaches in YOPD are lacking, and therefore our suggestions are based on indirect evidence. Several recent therapeutic algorithms for PD involved the age of patients as a variable (e.g. L-dopa versus dopamine receptor agonists) [40]. In their proposed strategy for symptomatic therapy in PD, Marras and Lang [56] included (1) a low threshold for initiation of treatment; (2) initiating treatment with L-dopa in patients over the age of 60 years; and (3) initiating treatment versus dopamine receptor agonists) [40]. In their proposed strategy neuroprotective effect of dopamine receptor agonists through their clinical studies in animal models of PD revealed an independent role in the disease in YOPD, it is important to mention that pre-receptor agonists. In the light of the expected long-lasting period of treatment, pramipexole or ropinirole than with L-dopa [58,59]. Due to different proposed explanations of such findings, it remains uncertain whether dopamine receptor agonists have neuroprotective effects in PD, although this possibility still remains. Finally, YOPD patients have an increased rate of depression [15]. It has been shown that some dopamine receptor agonists may also have antidepressive efficacy (e.g. pramipexole was comparable to sertraline 50 mg/day in some dopamine receptor agonists may also have antidepressive efficacy [15]). It has been shown that some dopamine receptor agonists may also have antidepressive efficacy [15].

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Conflict of interest

The author discloses: (a) honoraria for lectures on the treatment of PD for Novartis, Boehringer Ingelheim and Glaxo-Smith-Kline, and (b) serving as a member of the Regional, South-Eastern European Advisory Board of Boehringer Ingelheim.

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