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RECENT ADVANCES IN MANAGEMENT OF PARKINSON DISEASE

Neurology

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ABSTRACT

Management of Parkinson's disease (PD) is complicated due to its progressive nature, the individual patient heterogeneity, and the wide range of signs, symptoms, and daily activities that are increasingly affected over its course. The last 10–15 years have seen great progress in the identification, evaluation, and management of PD, particularly in the advanced stages. Highly specialized information can be found in the scientific literature, but updates do not always reach general neurologists in a practical and useful way, potentially creating gaps in knowledge of PD between them and neurologists subspecialized in movement disorders, resulting in several unmet patient needs. However, general neurologists remain instrumental in diagnosis and routine management of PD. This review provides updated practical information to identify problems and resolve common issues, particularly when the advanced stage is suspected. Some tips are provided for efficient communication with the members of a healthcare team specialized in movement disorders, in order to find support at any stage of the disease in a given patient, and especially for a well-timed decision on referral.

KEYWORDS

drug repurposing; immunotherapies; gene therapies; neural grafting; Parkinson's disease

1. INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease characterised by a movement disorder consisting of bradykinesia, rest tremor, and rigidity, along with postural instability, a range of other more-subtle motor features, and many non-motor features(Kalia and Lang,2015). Many of the core motor features result from the loss of a specific population of neurons: the dopaminergic neurons of the substantia nigra pars compacta, which project axons to the striatum(Dickson, 2012; Selhikova et.al,2009) . As such, most of the current pharmacological treatment approaches for PD aim to restore dopaminergic tone in the striatum.

Whilst often effective at improving motor function, current treatments are associated with significant side effects due to delivery of dopamine to extra-striatal regions, variability in their absorption and transit across the blood–brain barrier, and the non-physiological continuousrelease of dopamine and its effects on the dopamine receptors within the basal ganglia(Huot et.al,2013) . Patients frequently develop cognitive problems, levodopa-induced dyskinesias, and on-off fluctuations, which we have estimated to occur in 46%, 56%, and 100% of cases, respectively, at 10 years from diagnosis based on data from our ongoing community-based incident study in PD . All of these factors coupled with some of the neuropsychiatric features of PD have a significant impact on quality of life in advancing PD. Many features of PD (such as cognitive impairment and autonomic dysfunction) have a mainly non-dopaminergic basis, resulting from neurodegeneration at other sites in the central nervous system as well as the enteric and autonomic nervous systems . It is often these features that have the most detrimental impact on the quality of life of patients with PD, yet treatment options remain limited for these elements of disease.

1.1 Management according to the Disease Stage

Several studies support the early introduction of antiparkinsonian treatment as soon as the diagnosis is confirmed (Lohle et.al,2014). Oral levodopa, the initial gold-standard therapy for PD, is still the most effective and widely used therapeutic option in the treatment of this neurodegenerative disorder. However, its use eventually results in the development of motor fluctuations and levodopa-induced dyskinesia (LID) . Nearly 40% of PD patients develop LID after 4 to 6 years of levodopa treatment.

Therefore, particularly in younger patients in whom motor complications typically occur earlier and are more severe, pharmacological treatment should be started with MAO B inhibitors or dopamine agonists, adding levodopa later on as soon as needed.

1.1.1 Optimization of Conventional Oral Medication

Key messages for treatment of Parkinson's disease (initial stages) are as follows:

(i) When choosing medication, individual approach is required based on symptoms and preference.
(ii) Start low and go slow until reaching good clinical benefit
(iii) Medications with a more continuous stimulation profile, such as dopamine agonists or MAO- B inhibitors, are preferred in initial stages if appropriate for the clinical profile of the patient
(iv) Levodopa should not be avoided at all costs, even in initial stages. Consider levodopa if other medications are not indicated or not effective.

1.1.2 Advanced Therapies for Advanced Stages

Key messages for treatment of Parkinson's disease (advanced stages) are as follows:

(i) If good ON period is shorter than 3 hours, further adjustments of oral medications will most likely fail, and advanced treatments should be considered.
(ii) Indication of advanced treatment options *should not be* delayed if standard medications fail to control sufficiently motor fluctuations.
(iii) Do not delay referral *or contact* with a team specialized in movement disorders if advanced disease is suspected.

1.1.3 Nonpharmacological Interventions across All Stages

The main goal of any management should be to maintain acceptable levels of functioning and independence. In advanced PD, this can be achieved with a careful combination of drugs and supportive nonpharmacological therapy (Witt et.al,2017) in the context of collaboration between the GN, the MD specialist, and the multidisciplinary team. Supportive nonpharmacological management in advanced PD patients should include physical rehabilitation, psychological support, occupational therapy, speech, language and swallowing therapy, and nutrition , among other possible interventions. Balance and gait have been shown to improve with physical therapy and exercise, thus reducing the risk of falling .Physical activity has beneficial effects in PD, and forms that have shown benefit include aerobic exercise including dancing and treadmill training, resistance training, and traditional activities such as Tai Chi and yoga (Balsingh,2018). High intensity training may also improve the motor symptoms and limitations . Speech therapy has been successfully used to improve hypophonic and hypokinetic speech and related functions, such as swallowing problems associated with PD .Integration of medical and nonmedicaltreatments is most efficiently planned by members of a multidisciplinary team, usually established as part of tertiary MD centers.

2. OBJECTIVE OF THE STUDY

The aim of this paper is to study a practical overview of the most up-to-date information from the recent literature, as well as relevant issues in the management of Parkinson Disease.

3. Literature review

The article reviewed various therapies other than dopamine treatment like A2a antagonists: antiparkinson medication reducing the over reactivity of substantia nigra due to loss of dopamine; Levodopa/Carbidopa Intestinal Gel: an aqueous gel containing levodopa and carbidopa; stem-cell therapies like embryonic and adult stem cell can be act through several mechanism; acupuncture: reduced

the motor symptoms and other disease related factors; various antiparkinson medications like IPX066 and ND0611 are sustained release and transdermal patches which are transported to GIT through high nutrients and patches are found to be useful in increasing the concentration, half-life of levodopa, thus downs the threatening risk of PD. The future treatment for PD should be considered as they have less side-effect and better results than other treatment as they not only decrease the symptoms but also the incidences of PD. If the symptoms are diagnosed early patient should go for genetic therapy to relieve from the disease which not only reduce the progressive increase of symptoms and disease. Considering all therapies, future treatments shows the weightage in reducing the progressive increase of PD in patient. Though these treatments are proven to be effective in treatment but still more targeted tools and techniques are required which can specifically target the cause and thus lowers the graph and rating scale of PD(Chandra et.al,2017).

Recent evidence indicates exergame-based therapy has been widely proven to be feasible, safe, and at least as effective as traditional PD rehabilitation. Further insight into new sensors, best practices and different cognitive stadiums of PD (such as PD with Mild Cognitive Impairment), as well as task specificity, are required. Also, studies linking game parameters and results with traditional assessment methods, such as UPDRS scores, are required. Outcomes for randomized controlled trials (RCTs) should be standardized, and follow-up studies are required, particularly for motor outcomes (Garcia et.al,2019).Stoker and Barker (2020) As understanding of PD pathogenesis grows, novel therapeutic avenues are emerging. These include treatments that aim to control the symptoms of PD without the problematic side effects seen with currently available treatments and those that are aimed towards slowing pathology, reducing neuronal loss, and attenuating disease course. In this latter regard, there has been much interest in drug repurposing (the use of established drugs for a new indication), with many drugs being reported to affect PD-relevant intracellular processes. This approach offers an expedited route to the clinic, given that pharmacokinetic and safety data are potentially already available. In terms of better symptomatic therapies that are also regenerative, gene therapies and cell-based treatments are beginning to enter clinical trials, and developments in other neurosurgical strategies such as more nuanced deep brain stimulation approaches mean that the landscape of PD treatment is likely to evolve considerably over the coming years. In this review, we provide an overview of the novel therapeutic approaches that are close to, or are already in, clinical trials.

4. CONCLUSION

The progressive and multifocal nature of PD adds complexity to the management of this disease, with important and increasing prevalence in the aging population. Recent advances in the knowledge of PD provide growing insight not only into mechanisms of the disorder but also into greater understanding of patients' needs and the use of relevant tools to improve their QoL. General neurologists attending PD patients at any stage may benefit from a practical update of this knowledge. There is a lot that GNs can do for their PD patients in earlier stages, as well as in advanced stages, particularly when in good and timely communication with a multidisciplinary team, whether for advice, support interventions, or referral when necessary.

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