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A REVIEW ON PARKINSON'S DISEASE: AN OVERVIEW

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ABSTRACT

Parkinson's disease (PD) is one among the foremost common neurodegenerative disorders. Sources of knowledge Literature search using Medline with keywords paralysis agitans supplemented with previously published papers known to the author. There are significant recent advances wit0hin the understanding of the pathogenesis of the disease. There has also been a greater realization that the disorder could also be related to significant non-motor disturbances additionally to the more commonly recognized motor complications. Although there's growing indirect evidence, it remains to be proven whether any of the present treatments for PD have a neuro-protective effect. Although there's no cure, there are several management options for the first treatment of PD. because the disease progresses, further treatment options are available; however, the management of late-stage motor complications and non-motor symptoms remains particularly challenging and can enjoy further clinical research.

KEYWORD: Parkinson's disease, motor complications, non-motor complications.

INTRODUCTION

Parkinson's disease (PD) may be a common neurodegenerative disorder a synucleinopathy with a prevalence of 160/100000 in Western Europe rising to ~4% of the population over 80.1 with an ageing population, the management of PD is probably going to prove an increasingly important and challenging aspect of practice for neurologists and general physicians. Our understanding of the pathogenesis of the disease has been advanced within the last decade with the identification of several gene mutations which can shed light on the mechanisms of pathogenesis in sporadic cases of PD. The treatment of Parkinson's disease remains essentially a clinical one, and it's important to acknowledge the first features

alongside symptoms and signs suggesting other causes of Parkinsonism. There has also been a rapid expansion within the treatment options both within the early and within the later stages of the illness alongside a greater awareness of non-motor complications. Guidelines for the diagnosis and management of patients with PD are published from the National Institute for Health and Clinical Excellence (NICE) within the UK.[1,2]

Pathology, etiology and pathogenesis

The pathological hallmark of PD is cell loss within the nucleus Niger particularly affecting the ventral component of the pars compact. As the disease advances-Braak stages 3 and 4, the nucleus Niger, areas of the midbrain and basal forebrain get entangled. Finally, the pathological changes appear in the neocortex. This pathological staging is predicated on the distribution of lewy bodies. Lewy bodies are the pathological hallmark of PD. They are α-synuclein-immunoreactive inclusions made from variety of neurofilament proteins alongside proteins liable for proteolysis.[3] These include ubiquitin, a heat shock protein which plays a crucial role in targeting other proteins for breakdown. Mutations within the α-synuclein gene are liable for some familial sorts of PD during which lewy bodies also are seen. Mutations within the parkin protein produce a parkinsonian syndrome without lewy bodies in juvenile cases suggesting that the parkin protein plays a crucial role within the development of the lewy body. It has been shown that parkin facilitates the binding of ubiquitin to other proteins like the α-synuclein interacting protein synphilin-1 resulting in the formation of lewy bodies.[4] Lewy bodies are found in PD and Dementia with lewy bodies (DLB), but are not a pathological hallmark of any other neurodegenerative disease. The UPS is important for intracellular proteolysis and an outsized number of intracellular processes that maintain the viability of cells. It does this by removing unwanted proteins that are not any longer required by the cell. Failure of the UPS results in the abnormal aggregation of proteins including α-synuclein which are a serious component of lewy bodies. One of the primary sites for LB deposition in early PD is that the neural structure. It is, therefore, of interest that a disturbance in smell and taste is usually one among the earliest clinical features in PD raising the likelihood that LB formation may be integral for the activation of pathways resulting in neuronal dysfunction and death. The link between UPS and neurodegeneration has been strengthened by the invention of mutations in genes which code for several ubiquitin-proteasome pathway proteins in PD.[5]

Genetics of Parkinson's disease

Although PD is usually a sporadic disease, there are a growing number of single gene mutations which have been identified. At the time of writing, 11 genes have been mapped by genetic linkage with six genes identified: α-synuclein (SNCA), ubiquitin C-terminal hydrolase like 1 (UCH-L1), parkin (PRKN), LRRK 2, PINK 1 and DJ-1 genes. A point mutation of the SNCA gene leads to the early onset of PD in affected members in an autosomal dominant pattern. Of interest, duplication or triplication of the SNCA gene in affected members leads to PD symptoms developing at a later age in the fourth or fifth decades raising the possibility that overexpression of SNCA may be a factor in sporadic disease. The LRRK 2 gene (PARK8) is the most common cause of familial or the so-called 'sporadic' PD to date.8 The frequency of LRRK2 mutations in patients with a family history of PD is 5–7%. The heterozygous mutation, 2877510 g → A, produces a glycine to serine amino acid substitution at codon 2019 (Gly2019 ser). This LRRK2 G2019S mutation is the most commonly described, accounting for the majority of familial cases and up to 1.6% of cases of idiopathic PD, though the prevalence seems to be very variable. Lewy bodies have been identified in some LRRK 2 cases. Symptoms at onset may be typical of idiopathic PD characterized by unilateral bradykinesia and rigidity, with tremor present in some but not all patients. However, it is not possible to identify parkin positive young onset PD patients from parkin negative patients on clinical features alone. There has been a great deal of research into mitochondrial genetics and function in PD. Abnormalities in Complex 1 of the oxidative phosphorylation enzyme pathway is the most consistent finding, having been detected in PD brains, blood platelets and skeletal muscle, and other complexes have also been reported.9 It appears that the cells of the pars compact are particularly susceptible to oxidative damage. Mitochondrial DNA studies have as yet failed to identify a convincing gene mutation to explain the oxidative phosphorylation defects in PD. However, it seems likely that a mitochondrial defect may play a role in the pathways leading to cell dysfunction and death. The PINK1 gene codes for a mitochondrial complex and has been shown to be responsible for an autosomal recessive form of PD, though is not a major risk factor for sporadic disease.

Environmental factors

Identifying environmental factors that predispose to the event of PD has proved elusive. Living during a rural environment appears to confer an increased risk of PD, and maybe causally linked to the present some but not all epidemiological studies have shown a correlation between exposure to pesticide use and wood preservatives.10 the sole consistent

environmental factor may be a strong indirect correlation between cigarette smoking and therefore the development of the disease. It's also possible that mitochondrial dysfunction in PD is triggered by one or more environmental toxins.

Clinical diagnosis of PD

The features of Parkinson's disease are bradykinesia, rigidity and rest tremor. These may not all be present. Postural instability may be a feature, though early postural instability backwards particularly with a history of falls is more suggestive of progressive supranuclear palsy (PSP). The clinical findings are usually asymmetrical in PD. The clinical diagnosis may often appear straightforward, though it is worth noting that post-mortem studies have shown an alternative diagnosis in up to a quarter of patients with Parkinson's disease treated by general neurologists.[11] There are a number of other clinical signs that are worth highlighting. A change of handwriting with micrographia is often an early feature as is reduced facial expression. A loss of arm swing on one side is also an early and useful diagnostic feature. A glabellar tap does not seem to be particularly sensitive or specific. A reduced sense of smell is, however, worth asking about since this may be one of the first symptoms in early PD.[12,13] Adult onset dystonia may also present with asymmetrical rest tremor and may explain some patients previously labelled as 'benign tremulous PD' who have scans with no evidence of dopaminergic defecit.[14] Single photon emission computerized tomography (SPECT) imaging using a dopamine transporter (DAT) can be helpful in differentiating PD from a number of conditions, including essential tremor and dystonic tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism all of which demonstrate normal DAT scans. Uptake within the basal ganglia is reduced in PD, the parkinsonian syndromes and DLB.[15]

Management of early PD

After establishing a clinical diagnosis, it is vital to take time to explain the condition and its implications to the patient and relatives. This remains unresolved, despite a large number of *in vitro*, *in vivo* and human studies many of the latter using PET or SPECT imaging as surrogate markers of nigrostriatal dopaminergic function.[16] At present, therefore, there are no proven neuroprotective therapies with only symptomatic treatments available. Treatment in the initial stage is to alleviate symptoms allowing the individual to be fully independent and to carry out their normal daily activities. It is vital that treatment is well tolerated. For this reason, monotherapy is usually desirable. If patients can remain on treatment with minimal side effects, with a satisfactory reduction of symptoms and a feeling of well-being

that allows them to live independently and productively, then treatment has clearly been worthwhile. In patients with minimal or no disability, early treatment may still be initiated. One study has shown that self-reported health status using a Parkinson's Disease Questionnaire (PDQ)-39 at initial consultation and for up to 18 months was worse in untreated PD patients,[17] though the validity of the rating scale in this patient group has been questioned.[18]

Should treatment begin with levodopa, a dopa agonist or MAO-B inhibitor?

First line levodopa treatment

For 40 years, levodopa, combined with a peripheral decarboxylase inhibitor, has been regarded as the gold standard for the treatment of PD. It still remains in many respects the most efficacious drug treatment. Long-term levodopa therapy frequently leads to disabling side effects. Motor fluctuations are most strongly related to disease duration and dose of levodopa exposure, whereas dyskinesias are predominantly due to duration of levodopa treatment.[19] The development of drug-induced dyskinesias in PD seems to be associated with intermittent stimulation of dopamine receptors. Levodopa has a short half-life of 60–90 min, and pulsatile levodopa supply to a denervated striatum seems to be an important aetiological factor. In addition, the more severe the nigral neuronal loss is at the introduction of levodopa, the sooner adverse features are seen. A controversial issue has been whether levodopa could have a neurotoxic effect.[20,21] The goal of the study was to ascertain whether levodopa treatment affected the rate of disease progression. At the complete of a 2-week washout period, the UPDRS scores of patients treated with all three doses of levodopa were better than those of the placebo group in a dose-responsive pattern. Although this may hint at a neuroprotective effect, it is possible that the 2-week washout period was insufficient. This showed a larger decrease in striatal DAT binding in a dose–response pattern.

First line dopamine agonist treatment

There are six orally acting dopamine agonists available in the UK. ergot derivatives: bromocriptine, pergolide, cabergoline and lisuride; and two non-ergot drugs: ropinirole and pramipexole. The dopamine agonists were initially licensed for use in conjunction with levodopa in patients with advanced PD. Monotherapy trials have been undertaken comparing dopamine agonists with levodopa. The first such trial using bromocriptine in the 1980s showed a delay in the onset of dyskinesias with bromocriptine monotherapy comparison with levodopa therapy, but no effect with regards to the onset of motor fluctuations.[22] Trials of

the more recently introduced dopamine agonists showed a significant reduction in the development of motor complications in patients initiated on agonist monotherapy compared with levodopa.[23-25] However, in the published trials of ropinirole and pramipexole monotherapy, patients treated with levodopa showed improved UPDRS scores (parts II and III) compared with those on dopamine agonists, although during the trials, patient and physician assessments for the two arms were comparable. The side effect profile of the dopamine agonists is similar to levodopa, but confusion and hallucinations are more frequent than with levodopa therapy alone. The dilemma of first line treatment in PD is therefore this: dopamine agonists produce fewer motor complications and the same QoL scores, but the price for this is a higher incidence of side effects and reduced efficacy as determined by the UPDRS. There has been a general belief that the potential for side effects with dopa agonist monotherapy is much greater in elderly patients, but studies with the newer agonists do not bear this out and these drugs can be well tolerated in patients over 75 years. However, there have been increasing reports of non-inflammatory fibrotic degeneration of cardiac valves with the ergot agonists.[26,27] specifically cabergoline and pergolide, and for this reason, they are no longer recommended as first-line treatments. Regular monitoring including ESR, chest X-ray and 6-monthly echocardiography are recommended for those continuing on ergot-derived agonists. Commonly used non-ergot-derived dopamine agonists include ropinirole, pramipexole and rotigotine. An uncommon, but important, side effect most frequently reported to date with pramipexole is an increased risk of pathological gambling.[28,29]

First-line MAO-B inhibitors

MAO-B inhibitors were widely used following the DATATOP study.[30] for their proven efficacy in symptom improvement and presumed ‘neuroprotective’ effect. However, a subsequent study by The United Kingdom Parkinson's Disease Research Trial Groupfollowing over 700 patients with mild early PD appeared to show a significant increase in mortality in patients treated with selegiline and levodopa compared with levodopa alone or bromocriptine alone. This finding was not replicated in further studies which indeed suggested the opposite, a possible reduction in mortality.[31,32] A more recent meta-analysis of 17 randomized trials involving a total of 3525 patients came to the conclusion that MAO-B inhibitors reduce disability, the need for levodopa and the incidence of motor fluctuations, without substantial side effects or increased mortality.[33] Many of these studies have been of short duration and have not compared selegiline with initial treatment with a dopamine agonist. However, MAO-B inhibitors do have a potential role as first-line monotherapy in PD

patients. Studies using rasagiline, a novel MAO-B inhibitor, have demonstrated efficacy in early and advanced disease. The TEMPO wash-in trial gave results compatible with a disease modifying effect, although like the dopamine agonist studies cited above, additional work needs to be done to confirm a neuroprotective effect.[34]

The treatment of late motor complications of PD

After some years of stable, sustained response to levodopa therapy, most patients with PD experience fluctuations in motor performance, the effect of a single levodopa dose becoming progressively shorter (wearing-off phenomenon). Also, periods of immobility unrelated to times of levodopa supply occur in most advanced cases (on–off phenomenon). Levodopa-induced dyskinesias occur with increasing duration of therapy, and more than 50% of patients will begin to develop motor fluctuations and dyskinesias between 5 and 10 years after commencing levodopa with 20–30% developing dyskinesias after <2 years. In younger patients, the situation is worse, with almost all patients under the age of 40 developing motor complications after 6 years from the introduction of levodopa. Treatment of levodopa-induced dyskinesias remains unsatisfactory. Simply reducing the daily dose frequently renders patients rigid and immobile. Furthermore, choreic-dystonic involuntary movements appear as a concomitant of motor response to levodopa in most patients suffering from motor fluctuations. Dyskinesias are usually present during periods of maximum motor response (peak-dose dyskinesias) or during the entire ON phase (square wave dyskinesia), but a diphasic pattern, with dyskinesias present at the beginning and end of motor response, also exists. Peak-dose dyskinesias are related to high-plasma concentrations of levodopa and can be managed by fractionating levodopa doses. Amantidine has also been shown to reduce peak-dose dyskinesias. Long-acting dopamine agonists such as rotigotine may also be helpful by providing continuous dopaminergic stimulation. Biphasic dyskinesias occur when plasma levodopa levels are rising or falling. They often affect the lower extremities to a greater extent. They may be difficult to control, but may respond to higher levodopa doses or a fast-acting agonist such as subcutaneous apomprphine injection. Off-period dystonia also affects the lower limbs preferentially and is associated with periods of inadequate mobility. This may respond to a dispersible levodopa preparation or subcutaneous apomorphine injection. The pathophysiology of motor complications during chronic levodopa therapy (levodopa long-term syndrome) is only partially understood. Currently, the consensus is that they reflect both progression of the underlying disease and the effects of intermittent, pulsatile levodopa supply to a denervated striatum. A number of treatments have been used to reduce the

severity and frequency of motor complications. The dopamine agonists have shown beneficial effects in the reduction of 'off' time and a concomitant reduction in levodopa dose in the later stages of the disease. However, this has to be balanced against a possible increase in dyskinesias. Other side effects which are commoner include somnolence and hallucinations. It does seem that the more recent agonists such as pramipexole and ropinirole have benefit over bromocriptine by reducing 'off' time.[35,36] Amantadine, an NMDA receptor antagonist, was originally developed as an anti-viral agent. By chance it was discovered to have additional properties including efficacy in PD. There is evidence that amantadine can reduce the frequency of motor complications including freezing, 'off' periods and dyskinesias.[37,38] although the evidence for efficacy was felt to be insufficient in a Cochrane review.[39] There is, particularly in the elderly, a relatively high incidence of side effects which include confusion, hallucinations, ankle swelling and livedo reticularis. Parenteral administration of a dopamine agonist in the form of subcutaneous apomorphine[40] may be a useful adjunct to treatment by reducing 'off' time without increasing the tendency towards dyskinesias or confusion. Similarly, duodenal levodopa infusion therapy has been shown to reduce 'off' time, to improve motor function and improve QoL with no increase in dyskinesias in patients with advanced PD.[41]

COMT inhibitors

Entacapone may be a peripheral catechol-O-methyltransferase COMT inhibitor that enhances the action of aminoalkanoic acid de-carboxylase (AADC) inhibitors. Assuming that the quantity of distribution remains unchanged, the addition of entacapone increases the plasma half-life of levodopa by ~45% after each dose. Similarly, tolcapone produces a dose-dependent increase in levodopa half-life, albeit it's given independently of the levodopa dose regime. When entacapone or tolcapone are added to levodopa/AADC-inhibitor therapy, they inhibit COMT—one of the enzymes liable for the metabolism of dopamine—resulting in greater and more sustained plasma and central systema nervosum levels of dopamine than with levodopa/carbidopa alone, producing a protracted duration of antiparkinsonian action and subsequent improvements in motor function. COMT inhibition, therefore, translates into less fluctuation of levodopa plasma concentrations, in order that levels remain within the therapeutic range and enjoy each dose of levodopa are going to be prolonged. Tolcapone was originally withdrawn due to reports of hepato-toxicity, but has recently been re-introduced for restricted use under strict monitoring guidelines. this is often not the case with entacapone which is additionally available as a combined triple medication (with levodopa and an AADC

inhibitor) to enhance compliance. The introduction of a COMT inhibitor are often a secure and effective way of smoothing out fluctuations in motor response. COMT inhibitors reduce 'off' periods, prolong the 'on' time and permit a discount of the levodopa dose.[42] they are doing not, however, have a levodopa sparing effect. Entacapone and tolcapone are potent, specific and reversible COMT inhibitors that provide significant benefits, particularly in managing motor fluctuations in patients with late-stage paralysis agitans, when wearing off is a crucial factor. they're also likely to possess an increasing role within the earlier stages of the illness. A study is currently underway to work out whether the introduction of levodopa and entacapone together reduces the event of dyskinesias compared with levodopa alone.

The role of surgery in PD

The surgery used in Parkinson 's disease dates back over 50 years. Initially, this concentrated on lesion surgery usually in the form of pallidotomy which was shown to be successful particularly for levodopa-induced dyskinesias. the development came with the introduction of stimulators. The procedure most commonly carried to reduce bradykinesia, tremor and rigidity and which also reduces drug-related motor complications is bilateral subthalamic stimulation. This can produce very dramatic benefit. The operation is technically difficult, but in experienced hands the risk of adverse events is low. However, the infrastructure and support team required to assess, carry out and monitor patients limits the availability of this form of treatment. In terms of patients most suitable for treatment,[46] STN DBS tends to be performed in patients under the age of 75 without significant systemic co-morbiditiy and in the absence of obvious structural abnormality on MR imaging. Most patients will have had disease duration of at least 5 years to allow for other causes of atypical parkinsonism to become evident. Assessment of a patient for DBS requires assessment by an experienced multi-disciplinary team.[43-46]

Non-motor complications

With the progression of the disease, there are varieties of non-motor complications in PD that are often seen. In many cases, these aren't directly associated with involvement of dopaminergic pathways and should therefore develop even in patients where motor symptoms are well controlled.

Sleep and PD

Sleep disorders are frequent in PD. This includes both disturbed nocturnal sleep and excessive daytime somnolence. Nocturnal sleep disturbance occurs in 60–98% of patients and

correlates with disease severity and levodopa intake. Although the underlying pathology of PD could also be partially responsible, it's important to also exclude associated disorders like medication-related sleep disturbance including off-dystonia, depression, obstructive sleep apnoea, paradoxical sleep behavioral disturbance (RBD), periodic limb movements of sleep and restless leg syndrome (RLS). RBD may be a parasomnia characterized by the loss of normal striated muscle atonia during paradoxical sleep with prominent motor activity accompanying dreaming and is increasingly recognized in patients with neurodegenerative disease, particularly the synucleinopathies. there's evidence that its development can predict cognitive impairment in PD patients without dementia.[47] If troublesome, it's going to answer alittle amount of clonazepam in the dark. Daytime sleep events also are more common in PD. within the most extreme form, this will constitute sudden irresistible attacks of sleep attacks all of sudden.[48,49] These episodes are reported in patients on levodopa monotherapy alone, but are more frequent with the utilization of dopamine agonists, particularly ropinirole and pramipexole. Patients got to be counselled to prevent driving and to avoid operating machinery if these develop. These settle spontaneously because the offending drug is withdrawn.

Cognition in Parkinson's disease

Cognitive involvement in PD seems to be common. The frequency of overt dementia varies from study to review counting on definition, methods of cognitive assessment and population differences, but is of the order of 40% for all PD patients. Dementia in PD could also be associated with variety of pathologies. However, it seems to be the event of cortical lewy bodies and/or Alzheimer pathology which are most relevant. The cholinesterase inhibitors rivastigmine, donepezil and galantamine are shown in open studies to possess a modest benefit in cognitive function and within the amelioration of hallucinations and psychosis in patients with PD-related dementia, although robust evidence-based data are strongest at this point for rivastigmine and to a lesser extent donepezil.[50,51]

Dementia with lewy bodies or Parkinson's disease with dementia ?

There has been controversy over the differentiation of paralysis agitans with dementia (PDD) and DLB. An arbitrary cutoff is usually used—the 1 year rule—where a diagnosis of PDD is formed if extrapyramidal motor symptoms are present for 12 months or more before the onset of dementia and DLB if the onset of dementia precedes or occurs within 1 year of parkinsonism. Revised criteria for the clinical diagnosis of DLB are published.[52] These

believe the presence of a dementing process with additional core features of fluctuating cognition and variation in attention and application, recurrent visual hallucinations and parkinsonian features. Both DLB and PDD are characterized pathologically by the presence of lewy bodies, though in PDD patients there's greater neuronal loss within the nucleus niger whereas in DLB patients there is greater cortical beta-amyloid deposition. DLB patients are often less levodopa-responsive. Both conditions respond to cholinesterase inhibitors. For a recent update on the excellence between PDD and DLB, please ask the review by McKeith.[53]

Mood disturbance and PD

Depression is the most common mood disturbance in PD occurring with a prevalence of up to 50T and occurring at any stage of the illness. Patients should be screened for underlying metabolic disturbances like hypothyroidism which may be easily confused with a depressive illness. Depression, when diagnosed, can be treated with cognitive behavioral therapy and antidepressants including tricyclic's and short acting serotonin uptake inhibitors (SSRIs). There is evidence that pramipexole features a significant antidepressant action.[54-56]

CONCLUSION

PD is a common neurodegenerative illness. The treatment remains a clinical one, and there should be a high index of suspicion to exclude other causes of Parkinsonism. A large number of agents alongside surgical interventions are now available to treat early and late complications of PD. The Increasing attention is being given to the diagnosis and treatment of non-motor complications in PD. Future developments in PD are likely to specialize in the concept of disease modifying drugs which supply neuroprotection.

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