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Research Advances in Parkinson's Disease

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About the Study

It is interesting to reflect on the enormous advances that have been made in our understanding of the clinical features, etiology, pathology and pathogenesis of the Parkinson's disease and on the treatments that have become available for the sufferers of Parkinson's disease. Although suspected for many years, recent discoveries have confirmed that there are many causes of Parkinson's disease at least in terms of genetics. Prior to the identification of the first gene for familial Parkinson's Disease our understanding of the cause of Parkinson's disease was based upon epidemiological studies and biochemical analyses of post mortem brain samples. The former suggested that certain chemicals, e.g. pesticides, herbicides and some occupations e.g. farmers, teachers increased the risk for Parkinson's disease, although these finding were not reproduced in all studies. Biochemical studies identified mitochondrial dysfunction and oxidative stress as important components of pathogenesis; inflammation and protein handling were also recognized as contributing to neuronal loss. The discovery of alpha-synuclein mutations and multiplications as a cause of Parkinson's disease and that this protein was an important component of Lewy bodies focused attention as a contributor to Parkinson's disease. Subsequent findings again highlighted mitochondrial abnormalities as central to Parkinson's disease causation including the description of the mitochondrial proteins as Parkinson's disease-causing genes, and that parkin, another cause of familial Parkinson's disease had important mitochondrial interactions. The most common cause of Parkinson's disease identified to date is mutations of the LRRK2 gene. The G2019S mutation alone accounts for up to 5% of apparently sporadic Parkinson's disease in some other communities. Other genes will no doubt be discovered and it is very likely that association or "risk" genes will become recognized as important factors in Parkinson's disease causation. For instance, glucocerebrocidase mutations appear to be significant risk factor for Parkinson's disease.

Genetics clearly plays an important role in Parkinson's disease etiology. Although the environment may serve to modify penetrance and expression of these genes, major associations between environmental factors and Parkinson's disease await identification. The clinical phenotype of Parkinson's disease continues to be of major interest and recent attention has focused particularly on the Parkinson's disease prodome i.e. the development of symptoms and signs prior to diagnosis. It has become clear that a proportion of patients may experience a combination or permutation of olfactory loss, rapid eye movement sleep behavior disorder, depression, constipation and possibly impaired color vision discrimination. It is hoped that these clinical features, perhaps combined with biochemical or easily accessible imaging markers might constitute 'biomarkers' that could allow identification of at risk individuals who would be suitable for early treatment with neuro-protective drugs.

The diagnosis of Parkinson's disease remains a clinical one; based on the motor features of the disease. Imaging of the dopamine transporter for instance, may be useful to distinguish Parkinson's disease from essential tremor or dystonic tremor, but does not reliably separate the parkinsonian syndromes, e.g. multiple system atrophy or progressive supranuclear palsy from each other or from Parkinson's disease.

Study of the clinical progression of Parkinson's disease has also highlighted the non-motor symptoms as a major determinant of the quality of life of patients, as well as the need for institutional placement and life expectancy. Cognitive disturbances including dementia, confusion and hallucinations, depression and a range of Autonomic abnormalities can develop early in Parkinson's disease, but typically manifest later in disease progression. Treatment for these problems remains limited and unsatisfactory.

The treatment of Parkinson's disease remains focused on the motor symptoms and comprises mainly dopaminergic therapy. Levodopa is still the mainstay of treatment and can be combined with both dopa-decarboxylase and catechol-O-methyl tranferase inhibitors to increase its half-life and effectiveness. The timing of treatment initiation for Parkinson's disease has been a topic of interest and debate. Although traditionally treatment was withheld until the patient suffered sufficient disability, the availability of modern drugs and an increasing recognition that earlier treatment may confer long term benefit have shifted initiation to earlier in the disease course. Neuroprotection remains an important goal for Parkinson's research. Advances in our understanding of the etiopathogenesis of Parkinson's disease have provided a multitude of compounds that may have potential in slowing the progression of Parkinson's disease. The challenge is how to test these in patients and demonstrate a modification of the progression of the disease. In the absence of a recognized biomarker of disease progression other than clinical dysfunction, clinical trial design has turned to delayed start comparisons to demonstrate an effect with symptomatic agents. Trails of rasagiline have shown that this drug can provide a better motor outcome when given earlier rather than later. The mechanism of this effect remains open to debate.