

Research into Parkinson's Disease and its Relevance to Understanding Degenerative Neurological Disease

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Abstract

Although Parkinson's disease has been regarded primarily as a disorder of movement, there is evidence that a substantial proportion of sufferers also show impairment of cognitive function. The relationship between disordered movement and impaired cognitive function is of great clinical and theoretical importance. We have sought to clarify this relationship in the context of our own and other research. Our current study is a prospective comparison of cognitive function in patients with Parkinson's disease and a matched control group, of 15 years duration.

DSM III R diagnosis of dementia has been identified in a substantial proportion of the patients with Parkinson's disease but none of the control group. Further, patients with Parkinson's disease and some of the control group have shown lesser degrees of impairment. These findings demonstrate that dementia in patients with Parkinson's disease is not due to a coincident disease and that 'subcortical dementia' is not the sole cause of cognitive decline. The results are compatible with the notion that dementia in patients with Parkinson's disease is due to an interaction between a specific pathology and the loss of neuronal cells as a part of the ageing process.

Key words: *Parkinson's disease, Dementia, Neurodegenerative disease*

Introduction

Parkinson's disease (PD) has attracted the interest of psychiatrists for 2 reasons — first, the management of psychiatric complications of PD is clinically important and, second, the study of the disease gives insight into a range of psychiatric and neurological disorders.

As a trainee in psychiatry, I prepared a dissertation based on a retrospective study of the psychiatric syndromes associated with PD.¹ This experience led to an interest in PD, which has continued throughout my professional life. Research projects on various aspects of PD followed: the effects of levodopa on the mood of patients receiving treatment for PD;² cognitive impairment in PD;³ the effects of PD on driving skills;⁴ emotional lability in PD;⁵ facial expression in PD;⁶ and factors influencing survival in PD.⁷ Currently, work concerns cognitive impairment in PD and the methodological issues encountered in research into this field.⁸

This work has some relevance to the wider understanding of neurodegenerative disease and the story of the evolution of thinking in this field is both interesting and instructive.⁹

Current Research

Our current research is a prospective controlled study of the incidence of dementia in PD. Since 1985, a trial has included a group of 50 patients with PD and a control group of 50 people. PD was diagnosed using the UK Brain Bank Criteria.⁹ Controls were matched for age, sex, and premorbid intelligence. All patients were free of other major physical illness and all were assessed at intervals of approximately 9 months using a series of tests of intellectual function, premorbid intelligence, disability, severity of neurological symptoms, and mood. The diagnosis of dementia was made by the rigorous application of DSM III R criteria by blind raters and the results analysed by survival analysis.⁹

Of 83 subjects in whom a diagnosis of PD was sustained and who did not show dementia at the first assessment and 50 control subjects, 21 patients with PD and no control subjects have reached the criteria for dementia during a period of 12 years. A further 21 patients with PD and 8 control subjects have shown lesser degrees of cognitive impairment. The incidence of dementia in PD can be expressed as 46.9/1000 person years of observation. Age at entry to the study, age at onset of PD, duration of PD, and severity of PD were

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positively associated with the occurrence of dementia.⁹ These findings are consistent with our earlier findings¹⁰⁻¹¹ and echo the findings of studies from other parts of the world.⁹

Causes of Cognitive Impairment in Parkinson's Disease

During the past 35 years, the relationship between severe cognitive impairment and PD has been considered in 3 distinct ways — first, that the decline is due to a coincidental dementing illness such as Alzheimer's disease (AD), second, that it is the product of changes in the subcortical region of the brain in which both motor and cognitive functions are disturbed, and third, that it is the result of interactions between the pathological processes which occur in PD and other processes which lead to the death of brain cells of which age-related cell degeneration is the most important.

A Coincidental Disease?

When it became widely accepted that some patients with PD become severely cognitively impaired during the course of the disease, the most frequent explanation was that patients had a coincidental dementing disorder. This explanation was supported by post-mortem pathological examinations that showed changes resembling those seen in AD. This explanation was also in keeping with the then current concept of neurodegenerative diseases — that they were quite separate and that the neuropathological changes that accompanied them were, in some respects, specific. In these circumstances, the frequency of dementia might be expected to be similar to that in the general population.

Subcortical Dementia?

An alternative view that emerged in the late 1960s, and subsequently gained substantial support, was that cognitive impairment in PD was due to lesions in the subcortical region of the brain, which interrupted both motor and cognitive functions. Mortimer et al found impairment in 93% of a clinic sample in the USA.¹² Moreover, impairment was detectable at an early stage of the disease.¹² These findings led this group to suggest that the severity of cognitive impairment in PD follows a continuum with dementia at one extreme and impairment of a single cognitive function at the other, but with the majority of patients showing minor degrees of impairment.

Other workers have demonstrated the frequent presence of cognitive impairment in PD that is much milder than dementia, and is demonstrated by only using specialised tasks, which aim to assess discrete cognitive functions.⁹ However, it has long been recognised that some patients with PD show impairment similar to that seen in AD although frequently less severe. The recognition of such states, together with the occurrence of cognitive impairment in other disorders of movement associated with subcortical pathology, led to the concept of *subcortical dementia*, a form of intellectual

impairment of lesser degree than is typically found in AD but affecting several cognitive functions and normally associated with a disorder of movement. Although the concept of subcortical dementia had been discussed for some years, the syndrome was formally proposed by Albert et al.¹³ The main features described by these authors were “emotional or personality changes, impaired memory, defective ability to manipulate acquired knowledge, and a striking slowness in the rate of information processing.” This description bears a marked resemblance to the syndrome of *bradyphrenia* described in 1922 by Naville.¹⁴

Many issues have been raised as to the nature of subcortical dementia. First, whether subcortical dementia should be regarded as a clinical or a pathological concept. Second, whether the pathological changes envisaged as underlying the syndrome are restricted to the subcortical region of the brain and its immediate projections or whether pathological changes might be more widespread. A third concern is whether the pathological and clinical features are distinctly different from those seen more widely in dementing illness, or if the presence of clinical features of a movement disorder simply give the cognitive impairment a different character. Fourth, whether subcortical dementia is a stable condition rather than a prelude to more widespread disease and global dementia. Finally, whether the clinical syndrome is always indicative of structural changes in the brain or might be produced by drugs or functional psychotic illness.¹⁵ Opinion on these matters has ranged widely from scepticism as to subcortical dementia being a discrete entity at one extreme to full acceptance of the concept at the other.⁹

McHugh¹⁶ has gone further than Albert et al¹³ and suggests that the subcortical region subserves functions not only in motor and cognitive functions but also in the control and expression of mood. This researcher suggests that some syndromes arising from subcortical disease represent a *subcortical triad* of signs and symptoms. This combination of features is most convincingly seen in Huntington's disease. A difference between this concept and that of Albert et al is that the morbid disturbance of mood, which forms part of the triad, is only intermittently present, whereas the cognitive and motor features are persistent. Cummings suggests that the concept of subcortical dementia is applicable to disorders of movement to varying degrees.¹⁷ In the case of PD, this author suggests that cognitive impairment takes 3 forms: a form that is relatively mild and may meet the criteria for subcortical dementia, a form that is more severe showing wider impairment of cortical functions but pathologically distinct from AD, and a severe form that shows neuropathological changes in both the subcortical region of the brain and in the cortex, the latter of the type seen in AD.

Interaction of Specific and Age-related Factors

During the past 20 years, a different view of the place of cognitive impairment in PD has emerged. Appel proposed a neurochemical mechanism for the process of neurodegeneration

seen in AD, PD, and motor neurone disease (MND or amyotrophic lateral sclerosis).¹⁸ The general theme from this paper that 3 diseases, previously regarded as quite distinct, might be the result of similar processes was taken up by others. Calne et al argued that the same 3 diseases, AD, PD, and MND, are examples of the premature degeneration of groups of neuronal cells due to an interaction between a specific toxic process and the ageing process.¹⁹ The loss of neuronal cells associated with ageing is envisaged to be the common factor in the 3 diseases. A review of epidemiological, clinical, and genetic data led to the suggestion that similar factors from each of these realms are acting in the 3 conditions.²⁰ More recently, Calne has drawn attention to the fact that cell loss in PD affects many of the same sites in the brain as those that show cell degeneration in normal ageing.²¹ Indeed, in great old age, changes in appearance and function may include some of the changes seen in disorders of movement, namely a stooping posture, shuffling gait, difficulty in turning, unsteadiness, slowness, and loss of facial expression. Whereas the effects of normal ageing do not produce clinically recognised symptoms, in AD, PD, and MND, combined effects produce clinically declared syndromes.

These ideas raise several issues. Firstly, as each of these degenerative conditions progresses they become more alike in their manifestations. There is ample clinical evidence of this as both motor and cognitive changes are seen in PD, AD is frequently accompanied by parkinsonism in its later stages, and dementia is described in a minority of patients with MND. The amyotrophic lateral sclerosis parkinsonism dementia syndrome seen in Guam is an extreme example of the coincidence of the features of these 3 disorders. Secondly, the diagnosis of PD has become increasingly difficult as specific causes of types of parkinsonism have been identified. A relationship to other neurodegenerative disorders, previously regarded as distinct, may be one of the sources of diagnostic difficulty. Thirdly, the 3 examples cited are all of unknown aetiology, making separation on aetiological grounds impossible. Fourthly, the presence of a specific cause of cell loss may bring forward, in time, cell loss associated with the ageing process. In this respect, there may be a parallel with the AD type of dementia seen in patients with Down's syndrome, where the cognitive decline occurs earlier than would be expected in people of the same age who do not have Down's syndrome. Finally, the neuropathological changes observed in neurodegenerative disease may not be a good guide to the aetiology of the conditions concerned as they may be non-specific remnants of pathological processes for which many causes may be responsible.

How might these findings be interpreted in the light of these different hypotheses?

An Intercurrent Disease?

Our current study was primarily designed to establish whether dementia was more common in patients with PD than in healthy people and, secondarily, to examine the notion

that dementia in patients with PD was due to an additional pathology, such as AD, superimposed upon PD. Our study shows quite clearly that the incidence of dementia is greater in PD than in healthy controls of the same age, sex, and intelligence. This finding demonstrates that cognitive impairment in PD is not an incidental event but more likely to be an intrinsic part of the disease process underlying the syndrome of PD. However, at this stage we cannot be certain that our control subjects will not show a similar incidence of dementia at a later age. The study by Larsson et al in a general population showed an increasing incidence of dementia occurring with age but many subjects died before becoming demented.²² A similar pattern of deaths might be expected in our control group making it unlikely that the incidence of dementia would be as great as that observed in the PD group.

There are other qualifications that must be applied to our findings on account of certain details in our methodology. Our exclusion criteria for both index and control groups led to a study of subjects who were unusually healthy apart from 1 group with PD. This means that neither group can be taken as representative of the general population. Our study was designed to produce groups of subjects who differed only in one respect, namely whether they had PD or not, so that any observed differences during follow-up could be attributed to having PD or not having PD, although this limits other comparisons. For example, our exclusion criteria would be expected to reduce the likelihood of multi-infarct dementia in both groups and prevents us from studying this and other factors that may contribute to dementia in patients with PD. Despite these reservations, we can reject the hypothesis that dementia in PD is due to intercurrent illness with a high degree of confidence.

Subcortical Pathology?

Our study gives some information on the likelihood of cognitive impairment in PD being attributable to subcortical pathology. First, we observed that some subjects showed progression from mild impairment, compatible with Albert et al's description of subcortical dementia, to a level of severity that was incompatible with this designation.¹³ Secondly, study of the progression of impairment showed that some subjects, who eventually became demented, displayed impairment of higher functions of a kind generally attributed to cortical function at an early stage of the disorder.²³ Despite these observations, it is possible that some of our subjects with mild impairment have lesions only in the subcortical region of the brain — we hope to be able to clarify this at a later stage of the research from postmortem examination of the brains.

Interaction of Specific and Age-related Changes?

We have found a strong relationship between age and the liability to cognitive impairment and dementia at all stages

of our work. These findings are compatible with the third hypothesis. We have found evidence of cognitive impairment in control subjects but not yet of a severity that would merit a diagnosis of dementia. Impairment observed in the control group is occurring later than in the index group. This finding is compatible with the notion that the presence of specific lesions may bring forward in time other changes in brain structure and function. Our findings do not contribute to the discussions on the inter-relationships between PD and other degenerative disorders.

In Conclusion

We intend to delineate the natural history of cognitive function in PD by following our cohort of subjects until they have died. This data will enable us to estimate the risk of dementia in a clinic sample of patients with PD and to establish the factors that predispose them to dementia. With the introduction of drugs for the treatment of dementia, this information may be a guide to management. We hope to study the frequency of dementia in the control group as they age and see whether this reaches that of the index group but at a later age. This will be difficult as some of our control subjects have a substantial life expectancy. Patients with mild dementia in PD will be followed to see how often they progress to a more severe form and to study the nature of the changes that occur. Clinicopathological correlations will be possible in a proportion of patients, which may show whether the diagnosis of dementia is compatible with neuropathological lesions in the brain stem alone.

Our work and that of others in the same field demonstrates the need to be prepared to reinterpret information and to review the conclusions drawn. Progress in understanding requires the integration of findings from different disciplines, including epidemiology, nosology, clinical studies, psychology, genetics, pharmacology, toxicology, physiology, and neuropathology. Restriction to any one area of study may lead to erroneous conclusions.

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