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Predictors of Parkinson's disease dementia: Towards targeted therapies for a heterogeneous disease

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SUMMARY

Parkinson's disease dementia (PDD) has become an increasing area of research as treatments for the motor features of Parkinson's disease (PD) have improved and the population of patients with PD grows and ages. If predictors could be used to identify a sub-population of patients at risk of developing an early PDD then research into its neuropathological basis and treatment could be more effectively targeted to specific individuals. At present the predictors with the most evidence have arisen from longitudinal studies tracking the development of dementia in populations of incident, newly diagnosed patients with PD. Evidence exists for predictors across multiple domains: clinical, biological, neuroimaging and genetic. Some of the most robust of these suggest that PDD may develop as the result of an age and tau dependent, posterior cortically based process driven in some cases by mutations in the gene for glucocerebrosidase (GBA). It is clear, though, that more research needs to be undertaken into finding reliable predictors of PDD. At present the best approach may be to combine a set of predictors already identified in order to provide a basis for understanding why and how it occurs. Through this, new therapeutic strategies may emerge.

1. Introduction

Parkinson's disease (PD) is a heterogeneous neurodegenerative condition with a characteristic motor phenotype but also multiple non-motor manifestations. As options to ameliorate motor features improve, scrutiny has moved towards the non-motor characteristics of PD. Parkinson's disease dementia (PDD) is a critical non-motor evolution of PD. It is a key prognostic factor for entry to a nursing home and carries with it an increase in mortality [1].

In 2007 a taskforce set up by the Movement Disorder Society (MDS) came up with a set of clinical diagnostic criteria for probable PDD which require an established diagnosis of PD and a dementia syndrome of insidious onset for diagnosis [2]. Due to their relatively recent publication many cited studies have not used these criteria but they should help increase concordance between study results in the future.

The estimated prevalence of PDD varies but in a recent community based longitudinal incident cohort study the cumulative probability of developing dementia was 46 per cent by 10 years from diagnosis [3] with the number increasing to 80% at 20 years of follow up in a separate study [4]. This suggests that most patients with PD will end up with a dementia but that they reach it at different rates and if the factors underlying this could be elucidated, then novel targets for treatment may emerge which could then be matched to patients with fast and slow rates of conversion to PDD.

Being able to predict who will develop PD dementia, and when, needs to be robust and accurate long enough before it develops to provide an opportunity for intervention. It should also be easily measurable in a manner that is acceptable to patients and cost-effective for healthcare providers.

2. Heterogeneity of cognitive impairment within Parkinson's disease

To understand the search for predictors of PDD it is important to recognise the heterogeneous nature of cognitive impairments within PD. A theory that we have put forward is that cognitive impairments in PD can be broadly split into two independent processes, with the caveat that these may overlap in individual patients who have both processes going on at the same time. One process involves a dopaminergically mediated fronto-striatal based deficit of executive function which occurs throughout the disease and is driven by a complex interaction of disease stage, L-dopa dose and COMT genotype and which does not progress to dementia. On the other hand, there is a dopamine independent cognitive decline to dementia that involves a loss of posterior cortically based cognitive tasks and is related to age, tau haplotype, GBA gene status and possibly cortical amyloid-β [3,5–7]. In this review we will focus on this type of cognitive impairment, which some

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would term PD-MCI, although we would prefer the term prodromal PD dementia [8].

Whilst we will explore this aspect of PD dementia, there is a school of thought that the dementia in PD is also predicted by frontally based deficits of executive function or indeed a combination of cognitive deficits across a range of domains. In this respect an MDS task force was set up to draw up new guidelines to standardise all this into a diagnosis of PD-MCI, but predictor findings related solely to the broad criteria of PD-MCI will only be valid if it can be proven that PD-MCI in its current broad definition progresses to PDD, which at present is not certain [9]. For new data to be robust, correlations with PD-MCI are not therefore sufficient and longitudinal cohort follow up studies correlating predictors with clinical findings of progression to dementia are needed.

Finally it should be noted that PDD has historically been treated as a distinct entity from dementia with Lewy bodies (DLB) with regard to treatment and research. PDD diagnosis requires motor symptoms of PD to be present for one year before the dementia is diagnosed whilst DLB has the opposite temporal relationship but there is significant cross-over between the two diseases. Furthermore the distinction between PDD and Alzheimer's Disease (AD) has also become blurred with increasing evidence for overlap of pathology in a substantial number of patients [6,10]. Thus whilst we talk about PDD as a discrete entity, this is something of a simplification.

3. Clinical predictors of PDD

3.1. Age

Age has been shown to be an important predictor of PDD, dependent on the absolute age of a person with PD rather than the age of onset of the disease [3,4,11]. The influence of age, independent of disease duration, suggests a role for other pathology in addition to Lewy body disease in the development of PDD. In our own CamPaIGN study, the 10-year longitudinal follow up data found an association between PDD and MAPT genotype which influences tau transcription [3]. Another study found that greater cortical amyloid-β deposition and ageing may be closely related and together influence the onset of dementia in PD [6]. This all fits with the hypothesis that there is an overlap of pathologies (α-synuclein, tau and amyloid-β) in patients with PDD and perhaps with increasing age there may be more concomitant age-related pathologies present [10].

3.2. Motor features

Motor phenotype (tremor dominant [TD] versus postural instability and gait difficulties [PIGD]) appears to have a significant relationship to cognitive decline and the development of dementia in PD. In an 8-year prospective cohort study no patients with persistent TD disease developed dementia and their Mini Mental State Examination (MMSE) scores remained stable whereas those who had PIGD at baseline, or who converted to PIGD, had a significantly higher incidence of dementia and decline in MMSE score [12].

The progression from TD to PIGD phenotype is unidirectional and irreversible and symptoms show limited response to dopaminergic medication, similar to PDD, so it is postulated that this may indicate a common underlying spreading pathological process [12]. However in our CamPaIGN study, we found no significant overlap between motor phenotype and dementia for reasons that are not clear.

Although at present the relationship between the neuropathology of PIGD and dementia remains uncertain, a link to amyloid-β deposition and/or cholinergic pathways may exist. A recent cross-sectional study suggested a relationship between lower levels of cerebrospinal fluid (CSF) amyloid-β and a PIGD presentation [13], which links to a study showing that reduced CSF amyloid-β may be a predictor of dementia [14]. In addition, cholinesterase inhibitors have been shown to improve cognition in PDD [15] and reduce the risk of falls in PD patients with significant postural instability [16].

If a relationship exists between dementia and PIGD it is clearly complex but the presence of PIGD can be easily measured clinically and thus if further evidence emerges, it might be a useful predictor of PDD.

3.3. Cognitive features

Limbic and posterior cortical deficits have been shown to predict subsequent dementia. Impaired semantic fluency and pentagon copying at diagnosis of PD predicted dementia and rate of cognitive decline over 10 years in the CamPaIGN study [3]. In a smaller study conducted over 18 months, similar impairments in verbal learning, semantic fluency and silhouette-perception were also linked to the subsequent development of dementia [14].

In addition to providing practical neuropsychological predictive tests that can be easily undertaken at minimal cost, these findings also have implications for our understanding of the neuroanatomical pathology of PDD. Semantic fluency impairment is thought to represent temporal lobe dysfunction and impaired pentagon copying as a marker of visuospatial and constructional ability to represent parietal lobe dysfunction. These would support the concept of PDD being a posterior cortically based process with a cholinergic and dopaminergic element to it given the effects that drugs acting on these systems have in modifying the expression of these features [3].

There are also studies that have found correlations between frontal executive function and subsequent dementia [17]. However, phonemic fluency as a measure of executive function has not been shown to correlate with subsequent dementia in other studies and is instead thought to represent independent fronto-striatal, dopaminergic cognitive impairment [5,14]. This area is still controversial and further research is needed on it.

3.4. Other non-motor features

Rapid eye movement (REM) sleep behaviour disorder is characterised by loss of the normal atonia that accompanies REM sleep. In a small cohort followed over 4 years, the presence of REM sleep behaviour disorder (RBD) predicted the subsequent development of a dementia [18]. Indeed in this study, only patients with RBD developed PDD. A further study with a short follow up confirmed these findings, showing a significant relationship between clinically apparent RBD and the development of dementia in PD, though this time the development of dementia was not exclusive to patients with RBD. The authors posit that the significance of development of dementia only in those with clinical, rather than sub-clinical, RBD may reflect the spread of Lewy body pathology out to the limbic system [19].

Hallucinations are common in PD and LBD and have been used to differentiate Alzheimer's disease from them [2]. Visual hallucinations (VH) are associated with increased incidence of PDD as well as increased rate of cognitive decline (see e.g. [20]).

Despite no predictive link with PDD being established, it has been shown that autonomic symptoms including constipation, urinary incontinence, orthostatic hypotension and erectile dysfunction can precede the onset of PD or DLB by up to 20 years and are both common in PDD and a possible predictor of survival [21]. The implication of the presence of these autonomic features in PD is similar to that of the presence of dementia, namely it is a clinical expression of a more malignant spread of pathology to areas outside the substantia nigra.