COMBINED USE OF NEUROPSYCHOLOGICAL, BIOCHEMICAL, AND NEUROIMAGING BIOMARKERS FOR ASSESSMENT OF RISK OF DEMENTIA IN PARKINSON’S DISEASE

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Duration: 3 years
1. Summary of the project

Main objective: To study the potential interest for predicting dementia in Parkinson’s disease (PD) of the combined use of a series of biochemical (cerebrospinal), neuropsychological, and neuroimaging (MRI) biomarkers.

Specific objectives:
1. To characterise PD patients in terms of their neuropsychological performance, their levels of a series of cerebrospinal fluid (CSF) proteins, and their quantitative measures of the degree of brain atrophy.
2. To correlate these biomarkers with each other and with the clinical profile of the subject (healthy, PD non-demented, PD with dementia) with the hypothesis that control subjects will display normal values of these biomarkers in contrast to conspicuous alterations among the demented patients, with the non-demented ones ranking from normal findings to early abnormalities.
3. To determine the risk of dementia related to the studied biomarkers with the hypothesis that the subjects with PD with no dementia at baseline but with abnormal biomarker values will be at greater risk of evolving into dementia than those with normal findings.

Design:
1. Design and subjects: Cross-sectional and follow-up study: the former phase will be devoted to comparing healthy controls, PD patients with no dementia (PDND) and PD patients with dementia (PDD); the latter will try to ascertain whether any of the studied biomarkers or a combination of them is good at predicting conversion to dementia.
2. Procedures: All subjects will undergo lumbar puncture for measurement of CSF biomarkers, thorough neuropsychological testing, and quantification of the grey matter volume by means of voxel-based morphometry analysis of the MRI at baseline. The neuropsychological testing and the MRI will be repeated at 18 months for PDND subjects only.
3. Statistical analysis: Comparative and correlation studies will be performed at baseline and for the longitudinal data, for which regression models to
determine the risk of dementia for each of the studied biomarkers will also be used.

**Work plan:**

1. **First year:** recruitment and baseline studies of controls and PD patients.
2. **Second year:** completion of the recruitment and analysis and discussion of the cross-sectional results for their subsequent presentation to meetings and eventual publication; beginning of the first 18-month follow-up studies.
3. **Third year:** completion of the 18-month follow-up studies; analysis and discussion of the longitudinal data; submission of the results to international meetings and to international journals.
2. Results

a) Association between cerebrospinal and neuropsychological markers (cross-sectional phase)

We observed significantly higher CSF $\tau$ and phospho-$\tau$ levels in PDD than in PDND and controls, in association with memory deficits. In contrast, CSF $\beta$-amyloid ranged from high levels in controls to very low levels in PDD, with PDND subjects displaying intermediate (low to some extent) levels in association with verbal fluency deficits.

b) Association between cerebrospinal markers of sleepiness and dementia (cross-sectional phase) We failed to show any differences in CSF hypocretin levels (a biomarker of sleepiness in illnesses such as narcolepsy) between controls and PDND or PDD patients or any relationship with dementia, though demented patients had clinical and neurophysiological indicators of excessive sleepiness.

c) Association between cerebrospinal and MRI markers (cross-sectional phase)

We found a significant correlation between CSF $\tau$ and phospho-$\tau$ levels with grey matter volume reductions within the frontal and the temporal lobes which were in turn linked to memory deficits, whereas CSF $\beta$-amyloid levels were associated with white matter damage.

d) Association between cerebrospinal and genetic markers (cross-sectional phase)
We observed that certain tau gene polymorphisms imply high CSF τ and phospho-τ levels but only in the setting of low CSF β-amyloid levels and in the presence of dementia.

e) Association between the studied biomarkers and the risk of dementia (longitudinal phase)

We have been able to show that low baseline CSF β-amyloid levels significantly increase the risk of dementia and imply significantly greater MRI-measured grey matter volume reductions at follow-up.
3. Relevance and possible clinical implications of the final results

On one hand, our cross-sectional and longitudinal findings regarding CSF $\tau$ y $\beta$-amyloid levels and their associations with neuropsychological functions, quantitative MRI and gene polymorphisms reveal that PD patients with dementia have an Alzheimer-like profile. Furthermore, our data suggest that reduction of CSF $\beta$-amyloid precedes structural volumetric changes and determines the interaction between tau gene polymorphisms and CSF $\tau$ and phospho-$\tau$ levels. More importantly, low CSF $\beta$-amyloid levels are a risk factor for impending dementia in PD. This latter observation might imply CSF $\beta$-amyloid as an early risk marker of dementia and a potential tool to identify subjects eligible for testing specific molecular strategies, whereas if CSF $\tau$ and phospho-$\tau$ levels are confirmed to be increased only in later stages in the setting of dementia they might constitute surrogate markers of dementia for such clinical trials.

On the other hand, and as an additional contribution, our study of CSF hypocretin levels brings to an end the debate on whether excessive sleepiness in PD is narcoleptiform and on the potential usefulness of CSF hypocretin as a biomarker of sleepiness, dementia or advanced disease in PD. Our findings suggest that excessive sleepiness is a consequence of the progression and spread of the underlying neurodegenerative process, rather than merely a dysfunction of a single system (the hypocretinergic pathway).

4. Publications

*Cerebrospinal tau, phospho-tau, and beta-amyloid and neuropsychological functions in Parkinson's disease.*
*Mov Disord* 2009; 24: 2203-10. IF 4.014.

*Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in Parkinson's disease dementia.*

High cerebrospinal tau levels are associated with the rs242557 tau gene variant and low CSF β-amyloid in Parkinson disease.

Submitted or in preparation

Compta Y, Ibarretxe-Bilbao N, Junque C, Bargallo N, Braga-Pereira J, Valldeoriola F, Muñoz E, Tolosa E, Martí MJ.
τ and phospho-τ cerebrospinal levels correlate with temporal and frontal gray matter reduction in Parkinson’s disease and Parkinson’s disease with dementia.

Compta Y, Bargallo N, Tolosa E, Valldexoriola F, Muñoz E, Rios J, Martí MJ.
Posterior white matter hyperintensities are associated with low CSF β-amyloid in Parkinson’s disease.

Association between CSF τ and amyloid-β markers with neuropsychological, morphometric and clinical outcomes in Parkinson’s disease: a longitudinal study.