PLASMA AND NEUROPHYSIOLOGICAL MARKERS OF THE PROGRESSION OF COGNITIVE IMPAIRMENT TO PARKINSON'S DISEASE

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1. Project summary

The objectives of this project have been the characterization and progression of cognitive defects and neuropsychiatric disturbances in a sample of patients with Parkinson's disease without dementia, and their correlation with plasmatic, neuroimaging and neurophysiological markers, in order to be able to identify early markers of progression of cognitive impairment in Parkinson's disease.

Selected markers of plasma (microRNA, Nfl), neuroimaging and neurophysiological (potential evoked cognitive and resting-EEG) are characterized by the possibility to be generalized between different centres (both at a welfare and research level) and to be useful at the single patient level.

2. Obtained results

In order to achieve these goals, we recruited a new cohort of patients with Parkinson's disease (PD) without dementia (n = 105) and 55 healthy controls, and we have been following them for 2 years, with a loss of follow-up <10% of the basal sample.
At baseline, and during the follow-up, comprehensive neuropsychological and neuropsychiatric examinations were carried out systematically, plasma samples were collected, and cognitive evoked potentials were recorded both in patients and in healthy controls.

With this information we have been able to detect:

a. Patterns of neurophysiological dysfunction that characterize the state of mild cognitive impairment, as well as electrophysiological markers associated with the development of minor hallucinations, which at the same time appear to be a risk factor for the progression to PD dementia. In particular, the development of mild cognitive impairment is associated with increased latencies in PEVs N170 bilaterally, increased P3b latency, and both decreased amplitude and increased latency of the N400 wave. By using techniques of PEV generator localization (SPM, LORETA), we observed that these changes were located in temporal and temporal-parietal-occipital regions, which reinforces their role as markers of posterior cortical dysfunction, which has been

associated with progression of cognitive impairment in Parkinson's disease. The data are in the process of manuscript preparation (P3B, N170) and peer review in international journals (N400).

b. At the **neuroimaging** level, we have been able to define profiles of dysfunction of neural networks associated with both the development of mild cognitive impairment and minor hallucinations, and we have associated genetic alterations previously associated with a major impairment of cognitive impairment in PD with loss of cortical grey matter volume (COMT 158Val / Val, SNCA rs356181, MAPT H1H1). In particular, we have associated the development of the most initial cognitive defects of the disease to the progressive disruption of the ventral attentional network (anterior insula, dorsal anterior cingulate cortex) along with degeneration of the posterior regions of the default mode network (precuneus, posterior cingulate cortex). We have also observed the presence of minor hallucinations to be associated with loss of connectivity of regions of the default mode network with both the ventral and dorsal attentional network, along with hyperconnectivity of the posterior regions of the DMN with cortical regions involved in visual processing of motion in the peripheral visual field.

c. At the level of **biomarkers**, we are still in the process of final analysis. We have observed significant relationships between a greater rate of cognitive deterioration with microRNSa associated with oxidative stress. All these data are in the process of writing manuscripts.

3. Relevance with possible future implications:

The multimodal study at different levels (plasma biomarkers, neurophysiology and neuroimaging) in a cohort of patients followed longitudinally and systematically has a fundamental relevance to objectively differentiating the progression of cognitive dysfunction at the level of the individual patient (single patient level).

Given that cognitive and psychiatric disorders are associated with a faster rate of progression of the disease, these markers could be useful to identify individual patients with a more invasive form of PD.

Finally, since the markers found are associated with the dysfunction of specific brain regions and certain metabolic pathways, the selection of these patients will allow a more targeted molecular and genetic study, which could be relevant to identify specific therapeutic targets for the different subgroups of patients, which at the same time could ensure that clinical trials are directed to patients who can benefit from them at earlier stages.

All these findings are in line with the current perspective of personalized medicine, understanding that there is a variety of patients with a genetic and molecular differential substrate that requires individualized treatments for the same disease or syndrome.

4. Generated literature

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