DISEASE MODIFICATION IN NEURODEGENERATIVE DISORDERS – IS IT A VALID CONCEPT AND CAN IT BE STUDIED? NO

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There are a lot of expectations about the possibility to measure disease progression in Parkinson's disease (PD) and eventually come to the development of a disease modifier. Studies in at risk individuals are showing for the first time that PD may be identified before motor symptoms are clinical manifest and the Michael J Fox Foundation is launching the "Parkinson Progression Marker Initiative" (acronyms: PPMI) the largest clinical observational study so far, evaluating a cohort of recently diagnosed PD patients and healthy control subjects using multiple assessments to identify biomarkers of PD progression.
In terms of potentially effective drugs, rasagiline, a selective monoamine oxidase B (MAO-B) inhibitor initially registered for symptomatic control of motor fluctuations, has raised great hopes that neuroprotection or disease modification could be achieved. Enthusiasms were partially dampened after the publication of the first results of the ADAGIO study demonstrating that rasagiline 1mg/day, but not 2mg/day had a disease modifying effect. The study also raised some critical issues on the use of UPDRS as biomarker for disease progression and highlights the difficulties faced by current studies in early PD. In the attempt to administer rasagiline as early as possible the authors encouraged investigators to include patients immediately after clinical presentation. Indeed in ADAGIO, disease duration at study entry was as short as 4.5 months and mean motor UPDRS score was as low as 14,2. While this may be desirable because administration of a disease modifier agent should start as early as possible, inclusion of such mild cases which later proved to have little or no clinical progression, suggests that this observation was affected by uncertainties on clinical diagnosis.
I believe it is time to test the effectiveness of neuroprotective agents before symptoms have developed using a milestone event like development of motor disability as study end-point. Studies in patients with hyposmia or RBD have shown that abnormalities in dopamine nerve terminals can be detected in a significant percentage of subjects and that the rate of development of PD is 10% in 2-yrs in hyposmic subjects and 40-50% in individuals with REM Behavior Disorder (RBD) patients. This is giving us enough data to power a successful study. We also know that specific genetic mutations increase the risk to develop PD making carriers additional potential targets for neuroprotective drugs. By using imaging biomarkers like transcranial sonography to identify changes in substantia nigra echogenicity and dopamine transporter imaging to confirm presence of abnormalities in striatal dopamine nerve terminals we could identify a population were neuroprotection could be tested in a randomized placebo-controlled study. Moreover, such a study design would make the current debate on understanding the pattern of UPDRS deterioration as well as the potential influence of medications on Datscan binding unnecessary.