Abstract

Background
Cognitive impairment and motor dysfunction are common signs of sporadic and genetic forms of neurodegenerative diseases. Both symptom constellation and time to severe disability vary markedly between individual patients, not the least in Parkinson’s disease (PD). The incidence of non-motor features, including cognitive decline, is notably difficult to predict in PD. The reasons for this heterogeneity are mostly unknown.

Aims
To describe longitudinal clinical symptoms in patients with parkinsonism and cognitive decline with or without family history. To assess how clinical, genetic, and biochemical factors affect progression in neurodegenerative disorders with parkinsonism, and how these factors impact PD-subtyping systems.
Methods

Longitudinal clinical picture was described in two separate families with parkinsonism and cognitive decline. Genetic tests were carried out on patients and healthy individuals, looking for new or rare disease causes. A systematic review of previously published individuals with a known disease-causing point-mutation in the tau gene (MAPT p.R406W) was performed.

A cohort of approximately 140 PD patients were followed longitudinally through clinical examination and systematic survey of medical records. We will compare the prognostic capabilities of genetic and blood-based biomarkers and two PD-subtyping systems.

Preliminary results

In one family with an atypical, Alzheimer-disease-like form of frontotemporal dementia with relatively slow progression, we found a MAPT p.R406W point mutation. Radiological hallmarks of this disease were proposed, and we observed an unusual tau isoform pattern in neuropathology.

In the other family we will propose new candidate mutations for a dementing form of PD.

In the PD-cohort, approximately one third of the patients had developed dementia after a mean disease duration of 15 years. Upcoming results will inform on the clinical usefulness of PD-subtyping models. We will also assess whether combining genetic and blood-based biomarkers will improve the knowledge on subtypes of PD-progression further.

Impact

We summarized and expanded the knowledge on the MAPT mutation and the associated clinical picture. We will make suggestions to new genetic causes of familial PD. Developing and validating PD-biomarkers and subtyping systems are important today to prognosticate disease-course and will be crucial tomorrow for potential neurodegeneration-modifying treatments.

Published article to be included in the thesis


Slowly progressive dementia caused by MAPT R406W mutations: longitudinal report on a new kindred and systematic review.


Manuscript

Ygland E, et al.

Progression in Parkinson’s disease: Long term validation of clinical subtyping systems.