Alpha-synuclein in Parkinson's disease

Several studies have confirmed α-synuclein real-time quaking-induced conversion (αSyn-RT-QuIC) assay to have high sensitivity and specificity for Parkinson's disease. However, whether the assay can be used as a robust, quantitative measure to monitor disease progression, stratify different synucleinopathies and predict disease conversion in patients with idiopathic REM sleep behaviour disorder remains undetermined. The aim of this study was to assess the diagnostic value of CSF aSyn-RT-QuIC quantitative parameters in regard to disease progression, stratification, and conversion in synucleinopathies. We performed αSyn-RT-QuIC in the CSF samples from 74 Parkinson's disease, 24 multiple system atrophy and 45 idiopathic REM sleep behaviour disorder patients alongside 55 healthy controls, analysing quantitative assay parameters in relation to clinical data. αSyn-RT-QuIC showed 89% sensitivity and 96% specificity for Parkinson's disease. There was no correlation between RT-QuIC quantitative parameters and Parkinson's disease clinical scores (e.g. UPDRS motor) but RT-QuIC positivity and some quantitative parameters (e.g. Vmax) differed across the different phenotype clusters. RT-QuIC parameters also added value alongside standard clinical data in diagnosing Parkinson's disease. The sensitivity in multiple system atrophy was 75%, and CSF samples showed longer T50 and lower Vmax compared to Parkinson's disease. All RT-QuIC parameters correlated with worse clinical progression of multiple system atrophy (e.g. change in UMSARS). The overall sensitivity in idiopathic REM sleep behaviour disorder was 64%. In three of the four longitudinally followed idiopathic REM sleep behaviour disorder cohorts, we found around 90% sensitivity, but in one sample (DeNoPa) diagnosing idiopathic REM sleep behaviour disorder earlier from the community cases, this was much lower 39%. During follow-up, 14 of 45 (31%) idiopathic REM sleep behaviour disorder patients converted to synucleinopathy with 9/14 (64%) of convertors showing baseline RT-QuIC positivity. In summary, our results showed that αSyn-RT-QuIC adds value in diagnosing Parkinson's disease and may provide a way to distinguish variations within Parkinson's disease phenotype. The quantitative parameters however did not correlate with disease severity in Parkinson's disease. The assay distinguished multiple system atrophy patients from Parkinson's disease patients and in contrast to Parkinson's disease, the quantitative parameters correlated with disease progression of multiple system atrophy. Our results also provided further evidence for αSyn-RT-QuIC having potential as an early biomarker detecting synucleinopathy in idiopathic REM sleep behaviour disorder patients prior to conversion. Further analysis of longitudinally followed idiopathic REM sleep behaviour disorder patients is needed to better understand the relationship between αSyn-RT-QuIC signature and the progression from prodromal to different synucleinopathies [1)].

The main neuropathological finding of Parkinson's disease is Alpha-synuclein-containing Lewy body and loss of dopaminergic neurons in the substantia nigra, manifesting as reduced facilitation of voluntary movements. With progression of PD, Lewy body pathology spreads to neocortical and cortical regions. Several environmental factors are associated with increased risk of PD. Autopsy studies show that the clinical diagnosis of PD is not confirmed at autopsy in a significant proportion of patients. Revised diagnostic criteria are expected to improve the clinician´s accuracy in diagnosing PD. Increasing knowledge on genetic and environmental risk factors of PD will probably elucidate the cause of this disease within the near future [2)]

1)

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2)

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