Scottish Government Health Directorates Chief Scientist Office

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# Development of disease-specific diagnostic test for Lewy body dementia based on RT-QuIC analysis of cerebrospinal fluid.

## Researchers

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## Aim

Lewy body dementia (LBD) accounts for approximately 10% of all cases of dementia. It is commonly mistaken for Alzheimer's disease (AD) and is under-diagnosed. LBD is characterised by tiny deposits of a protein called alpha-synuclein (A-S) within the brain. The measurement of A-S concentrations within the cerebrospinal fluid (CSF) has been proposed as a diagnostic test for LBD, however several studies have shown that is it not very sensitive. Firstly, our aim was to use a recently developed technique called real-time quaking induced conversion (RT-QuIC) to create a new diagnostic test for LBD and secondly, to evaluate how good it is in distinguishing between LBD and AD.

## Project Outline/Methodology

RT-QuIC exploits the ability of A-S to change shape and aggregate together. Once aggregated A_S binds a fluorescent marker and fluorescence ca be monitored in real-time. We used a variety of recombinant A-S proteins as a substrate for RT-QuIC and a number of different reaction conditions to optimise the fluorescence response from brain material and CSF samples from patients with LBD. Once we developed a workable RT-QuIC technique we evaluated how useful it was by analysing CSF samples from patients who had LBD, AD or no evidence of dementia at post-mortem (control subjects). In addition we also tested CSF samples from patients who had neuropathological evidence of both AD and LBD.

## Key Results

A robust and reliable RT-QuIC assay for A-S was developed. A retrospective study of CSF samples taken during life from dementia patients and control subjects who underwent neuropathological examination at post-mortem. We analysed a total of 79 CSF samples: 12 from pure LBD patients (no evidence of AD neuropathology); 30 patients with pure AD (no evidence of LBD neuropathology); 17 patients with mixed LBD/AD at post-mortem and 20 control subjects. We found that 11 of the 12 (92%) patients with pure LBD had positive RT-QuIC responses and 10 of the 17 (59%) AD/LBD patients had a positive RT-QuIC response. None of the 20 control subjects or 30 pure AD patients had positive RT-QuIC responses. Therefore the sensitivity of the A-S RT-QuIC was 92% for pure LBD and 59% for mixed LDB/AD and the specificity was 100%.

## What does this study add to the field?

This is the first report of an aggregation assay for A-S that works with both brain and CSF samples from LBD patients. It has better discriminatory potential than the conventional immunological techniques that measure CSF A-S concentrations. The A-S RT-QuIC technique developed is robust and reliable.

## Conclusions

We found A-S RT-QuIC to be an accurate CSF diagnostic test for LBD, particularly when discriminating between LBD and AD.

## Implications for Practice or Policy

The A-S RT-QuIC described has the potential to be a new approach to the clinical investigation of patients with suspected LBD. It also has the potential to be used in other alpha-synucleinopathies such as Parkinson's disease.

## Where to next?

We are undertaking a second blinded retrospective study to confirm these findings with the aim to publish these results as soon as possible. We have also secured funding from the Michael J Fox Foundation to investigate the potential use of RT-QuIC in the investigation of patients with Parkinson's disease.

## Further details from:

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