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PRION DISEASE

# New approaches to CJD diagnosis

Creutzfeldt–Jakob disease (CJD) is a difficult condition to diagnose during a patient's life, but cerebrospinal fluid (CSF) biomarkers are beginning to emerge that are capable of differentiating CJD from other neurodegenerative diseases with high sensitivity and specificity. In two new papers, published in *Annals of Neurology* and *PLoS ONE*, respectively, Alison Green, Lynne McGuire, Byron Caughey and co-workers explore the potential of a recently developed prion protein conversion assay as a diagnostic test for sporadic CJD (sCJD), and Patrick Oeckl, Boris Ferger and colleagues identify the cyclic nucleotides cAMP and cGMP as possible CSF biomarkers for CJD.

Green explains that existing diagnostic tests, such as EEG, MRI, and 14-3-3 protein detection in the CSF, are not specific for sCJD, and might show variable sensitivity between disease subtypes. "sCJD can be transmitted from patient to patient through the use of contaminated surgical instruments, and the introduction of a disease-specific test would reduce this risk," she points out.

Green and her team from the National CJD Research & Surveillance Unit in Edinburgh, UK, used real-time quaking-induced conversion (RT-QuIC) to test for presence of the abnormal prion protein $PrP^{Sc}$ in CSF samples from 123 patients with neuropathologically confirmed sCJD and 103 controls. "This technique exploits the ability of the abnormal form of prion protein to convert recombinant PrP into a proteinase-K-resistant form in a cyclical manner," she explains. The conversion reaction is monitored in real time by use of the fluorescent marker thioflavin T.

The researchers found that RT-QuIC was considerably more specific than the CSF 14-3-3 assay for the diagnosis of sCJD (99% versus 65%), whereas the sensitivities of the two techniques were similar (89% for the 14-3-3 assay versus 94% for RT-QuIC). Importantly, the sensitivity of RT-QuIC was not affected by disease subtype or stage. "All these factors suggest that RT-QuIC is a highly specific test for sCJD that may enable earlier and more-accurate clinical diagnosis," concludes Green. "We are working to improve the diagnostic sensitivity of RT-QuIC and to adapt the technique for use with variant CJD CSF samples."

In the second study, Oeckl and colleagues used liquid chromatography coupled to tandem mass spectrometry to measure concentrations of cAMP and cGMP in CSF samples from 15 patients with CJD, 14 patients with amyotrophic lateral sclerosis (ALS), and 19 patients with either Parkinson disease (PD) or PD dementia (PDD). Each of these three groups was compared with a different age-matched control group. "We are the first to measure cAMP and cGMP concentrations in the CSF of PDD and CJD patients," says Oeckl.

The team detected no differences in cAMP and cGMP levels in the CSF of patients with ALS, PD or PDD compared with controls, but in patients with CJD the concentrations of these two compounds were reduced by 70% and 55%, respectively. These findings indicate that cAMP and cGMP measurements might be useful additions to the diagnostic arsenal for CJD.

"In the clinic, cAMP and cGMP might be used as markers of CJD progression or even as therapy control," says Ferger. "Especially, cAMP could be helpful in the differential diagnosis of CJD and AD, because another study has shown that cAMP increases in the CSF of patients with AD, in contrast to the decrease in CJD shown in our study." In addition to exploring the potential of cAMP to discriminate CJD from AD, the team intends to confirm the current findings in further studies with a larger cohort, including CJD patients at different disease stages.

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**Original articles** McGuire, L. I. *et al.* RT-QuIC analysis of cerebrospinal fluid in sporadic Creutzfeldt–Jakob disease. *Ann. Neurol.* doi:10.1002/ana.23589 | Oeckl, P. *et al.* CSF concentrations of cAMP and cGMP are lower in patients with Creutzfeldt–Jakob disease but not Parkinson's disease and amyotrophic lateral sclerosis. *PLoS ONE* **7**, e32664 (2012)

**Further reading** Atarashi, R. *et al.* Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion. *Nat. Med.* **17**, 175–178 (2011)