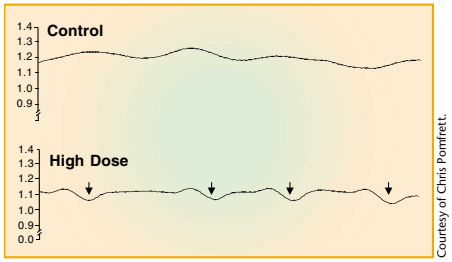
Heartbeat clue to diagnosing vCJD

Chris Pomfrett and colleagues at the University of Manchester, UK, may have found the Holy Grail of prion research: a simple, non-invasive test to diagnose patients with variant Creutzfeldt-Jakob disease (vCJD) before clinical symptoms show themselves.

The technique—a high-resolution electrocardiogram (ECG)—can identify a unique heart rate–variability signature caused by the early stages of infection. The test successfully predicted bovine spongiform encephalopathy (BSE) infection in cows before they showed signs of disease, and will now be tested on suspected human vCJD patients in the UK.

Currently, the only definitive means to diagnose BSE and vCJD—which are among a group of prion-based infections known as transmissible spongiform encephalopathies (TSEs)—is by postmortem examination of brain tissue. Detecting vCJD before patients show clinical symptoms is an urgent priority, as it could dramatically reduce the risk of contaminating blood supplies and hospital equipment and give patients and families time to prepare for illness. There have been 110 deaths to date from vCJD in the UK

Designing TSE diagnostic tests has been a challenge not only because it is difficult to find antibodies that penetrate the complex, folded structure of the abnormal prion, but also because prions have no genetic material to identify. The ECG test, called Fathom, aims to circumvent these problems by detecting a condition called respiratory sinus arrhythmia (RSA). Fathom measures beat-to-beat variability in heart rate with respect to breathing, and was originally designed to assess depth of anesthesia during surgery. Pomfrett decided to test whether RSA was affected in BSE-infected animals, on the basis of the idea that TSE infection passes from the gut along the vagus nerve into an area of the brain stem called the solitary nucleus, an area that controls RSA.



Tachygrams show heart rate variability in BSE animals

The team measured the heart-rate variability under laboratory conditions of 150 cows that had received either single low dose, a single high dose or no dose of BSE. Pomfrett told *Nature Medicine* that 2 animals that later died from the disease both showed increased levels of RSA as compared with controls, and this ECG pattern was detected 8 months before the animals died. Also, the higher-dose animals showed a statistically higher level of RSA than those that had received the lower dose. "Of the 700 patients that I have seen under anesthesia, I've never seen the effect to be so dramatic," said Pomfrett.

BSE appears to be the only brain-stem disease that increases sinus arrhythmia—other neurodegenerative diseases, such as Parkinson's disease, reduce it—making Fathom a potentially invaluable diagnostic tool. "One possible reason for this [may be] that once the dorsal vagal motor nucleus, which is involved in blood pressure control, is knocked out by TSE infection, the brain stem becomes unstable and the autonomic nervous system compensates by inducing sinus arrhythmia to try and maintain the blood pressure control," suggests Pomfrett.

For human trials, a 5-minute ECG recording and breathing information will be taken from the 7 people currently suspected of having vCJD in the UK, who will be monitored to see if the worsening of symptoms can be predicted.

The study is one of 22 being funded through a £7 million ($10 million) grant from the UK Public Funders of TSEs Research and Development group. Five other projects will try to identify whether 'surrogate markers', such as levels of manganese and tau protein in cerebrospinal fluid, are linked to TSEs. Other studies will look more closely at infectivity, at how possible transmission risk can be assessed and at methods to assess the effectiveness of decontamination procedures for surgical instruments.

Simon Frantz, London

TSE threat to US increases

The US Department of Agriculture last month confirmed that two sheep taken from a farm in Vermont were infected with a form of transmissible spongiform encephalopathy (TSE). Further tests are being carried out to determine whether the disease is bovine spongiform encephalopathy (BSE) or scrapie. The sheep were imported from the Netherlands (*Nature Med.* **6**, 1301; 2000). Analysis will take at least two years, and if the prion is that which causes BSE, this would be the first case of disease in the US.

Aguzzi warns of CWD danger

The TSE family of diseases also includes chronic wasting disease (CWD) in deer, a condition that has spread in the US in recent years (*Nature* **416**, 569; 2002). Speaking at the *Days of Molecular Medicine* conference in La Jolla in March, prion expert Adriano Aguzzi issued a strong warning against underestimating this form of TSE. "For more than a decade, the US has by-and-large considered mad cows to be an exquisitely European problem. The perceived need to protect US citizens from this alien threat has even prompted the deferral of blood donors from Europe," he said. "Yet the threat-from-within posed by CWD needs careful consideration, since the evidence that CWD is less dangerous to humans than BSE is less-than-complete.

Aguzzi went on to point out that CWD is arguably the most mysterious of all prion diseases. "Its horizontal spread among the wild population is exceedingly efficient, and appears to have reached a prevalence unprecedented even by BSE in the UK at its peak. The pathogenesis of CWD, therefore, deserves a vigorous research effort. Europeans also need to think about this problem, and it would be timely and appropriate to increase CWD surveillance in Europe too." Aguzzi has secured funding from the National Institutes of Health to investigate CWD, and the effort will be lead by Christina Sigurdson in his department at the University of Zurich.

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