vCJD: 30 years later

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Thirty years old, a crisis took hold of British farming when it was discovered that bovine spongiform encephalopathy (BSE) in cows could leap the species barrier from cows to humans. Mark Greener examines the nature of vCJD and whether any cure is in prospect.

In December 1984, cattle on a farm in Sussex began exhibiting unusual symptoms, including arched backs, losing weight, head tremor and lack of coordination. ‘Mad cow disease’ inevitably proved fatal. By the end of 1986, pathologists had identified the cause – bovine spongiform encephalopathy (BSE), transmitted between cattle through contaminated animal feed. The BSE crisis probably cost the UK economy more than £3.5 billion.1,2

In 1990, Conservative Agriculture Minister John Selwyn Gummer and his young daughter famously ate hamburgers in front of the media in an attempt to allay fears about the safety of British beef.3 However, researchers discovered in 1996 that BSE could leap the species barrier causing variant Creutzfeldt-Jakob disease (vCJD) in humans.

Since then, doctors in at least 12 countries – including France, Holland, Portugal, Spain, America and Italy – have identified patients with vCJD.4 However, the UK bore the brunt of the crisis. Between 1995 and 2014, 177 people in the UK died from vCJD, according to the National CJD Research & Surveillance Unit (NCJDRSU). Statistical modelling suggests that vCJD peaked about 2000 when there were 27 diagnoses and 28 deaths.5 In contrast, between 2012 and 7 April 2015, one person died from vCJD, NCJDRSU reports.

While the headlines and hype have largely subsided, there’s no room for complacency. A study of 32 441 appendixes from 41 UK hospitals found that 16 tested positive for vCJD, suggesting a prevalence of 493 per million of the population.6 In other words, about one in every 2000 people may harbour the abnormal protein that causes vCJD.7 Giving oral evidence to the House of Commons Science and Technology Committee in 2013, John Collinge, Professor of Neurology at the UCL Institute of Neurology and Director of the MRC Prion Unit, added that the test’s sensitivity is not known and could significantly underestimate the number of people infected with vCJD.7 Prion diseases can lurk undetected in the body for decades, raising the prospect that asymptomatic people will transmit the infection.8 ‘I think there is a significant problem,’ Professor Collinge said. ‘We do not know at the moment how many of those people will go on to develop the disease in the half century ahead in which this will evolve.’7

A family of related diseases

BSE is one of several related ‘transmissible spongiform encephalopathies’. In the early 1980s, researchers established that deposits of abnormally folded proteins – called ‘proteinaceous infectious’ (prion) agents – caused CJD and BSE.9 Prion deposits damage the surrounding tissue and seed further aggregations of the misshapen protein. So, the deposits spread the damage through the brain.10

Since the pioneering studies into vCJD and kuru,11 biologists have linked aggregations of misfolded proteins to a growing number of conditions including: Parkinson’s, Alzheimer’s and Huntington’s diseases; type 2 diabetes mellitus; amyotrophic lateral sclerosis; systemic amyloidosis; sporadic fatal insomnia, and variably protease-sensitive prionopathy (VPSPr).8,11-14 And prion diseases affect a zoo’s worth of species, including mink, sheep, goats, deer and elk.9

CJD arises from abnormal aggregations of a misfolded cell membrane glycoprotein, the prion protein (PrPSc). Neuronal cells in the brain produce most of the body’s PrPSc, but several other tissues express the protein at lower levels. While PrPSc is highly conserved across species, biologists do not fully understand the protein’s biological roles. However, PrPSc may contribute to synaptic activity, neuroprotection, nerve fibre organisation and resistance to oxidative stress.8

The misfolding produces a ‘highly infectious’ form of the protein (PrPSc) that tends to arrogate and can, in humans, cause sporadic, familial and acquired prion disorders.8 Between 1990 and 7 April 2015, for example, 1618 people died from sporadic CJD (sCJD), 170 from familial CJD and 79 from iatrogenic CJD. Overall, between 2000 and 2014, 67 to 118 people died each year from one of CJD’s four forms, according to NCJDRSU.
The clinical pattern

Most human prion diseases show common characteristics, including spongiform vacuolation throughout the cerebral grey matter, reactive proliferation of astrocytes and microglia, neuronal loss and, in some types, deposition of amyloid plaques. However, the prion diseases differ in several ways.

For example, patients with vCJD typically show widespread involvement of lymphoid tissues, with the prion present in the appendix, spleen and tonsils. Other human prion diseases do not show this more diverse lymphoid pattern. vCJD symptoms emerge at a median age of 28 years, compared with, on average, 60-65 years of age with sCJD. Death follows in an average of 14 months of vCJD symptoms emerging, compared with a mean of four months for sCJD. As a final example: about two-thirds of patients with sCJD show ‘generalised periodic sharp wave complexes with triphasic morphology’ on electroencephalograms. People with vCJD rarely show these complexes and only in the terminal stages.

Clinically, vCJD begins with psychiatric symptoms – including depression, delusions, and anxiety – that persist for about six months. Neurological features – typically confusion, ataxia, and choreiform, dystonic or myoclonic involuntary movements – develop rapidly. MRI shows a strong signal in the pulvinar region of the thalamus, the so-called hockey stick sign, on fluid attenuation inversion recovery. More than 90% of vCJD patients show diffusion-weighted imaging. The combination of core clinical features, MRI and pathology offers highly sensitive and specific diagnostic criteria.

vCJD can follow several clinical courses, partly reflecting patients’ genotypes. A gene (PRNP) on the short arm of chromosome 20 encodes PrPC. Around half (47%) of the UK population are heterozygous at codon 129 of PRNP, with methionine and valine (129MV), while 42% are homozygous for methionine (129MM) and 11% for valine (129VV). To date, all UK patients with definite and probable clinical vCJD have expressed 129MM. This suggests ‘an association between vCJD susceptibility and genotype’. However, people with 129MV and 129VV might have longer asymptomatic incubation periods than those with 129MM. Indeed, acquired prion diseases in general tend to have prolonged, asymptomatic incubations. Kuru can incubate in humans for more than 55 years, for example. Incubation periods are typically even longer when the prion spreads from another species.

Treatment remains elusive

Although studies have assessed several vCJD treatments, an effective therapy, let alone a cure, remains elusive. In animal models, pentosan polysulphate emerged as a possible treatment. However, pentosan polysulphate is administered by intravenous infusion, which requires neurosurgery. A ‘small number’ of vCJD patients treated with pentosan polysulphate showed extended survival. However, patients continued to decline and show severe neurological deficits.

In the future, monoclonal antibodies might offer a potential treatment for vCJD. In animal studies, antibodies targeting PrPSc reached mouse brain cells after intravenous administration. Obviously, further studies are needed, but the finding could aid the design of treatments for prion diseases and other neurodegenerative diseases.

Even if these developments reach the clinic, prevention and surveillance remain critical. For example, by 2004, researchers had recognised that blood from vCJD-infected humans could harbour prion infection. Therefore, a symptomatic patient could, theoretically, transmit the prion in blood transfusion or products. As a result, researchers developed screening assays, diagnostic tests and prion reduction filters. There have been four vCJD cases transmitted by blood, all of which seem to have occurred before the introduction of leukodepletion, which removes white cells.

Professor Collinge remarked that, ‘blood is the major issue in public health terms’. However, CJD also spread during medical and surgical procedures, from, for example: inadequately sterilised neurosurgical instruments; dura mater and corneal grafting, and gonadotropin or growth hormone derived from cadavers. So, the NHS currently runs ‘enhanced surveillance’ of about 5000 people who have been notified as being at increased risk of iatrogenic CJD. Doctors inform the patients about the exposure and ask them to follow precautions to avoid transmission. Such surveillance is probably ‘necessary for the foreseeable future’. For example, a second wave of vCJD might arise depending on, for example, genetic susceptibility, subclinical infection leading to secondary transmission, or in ‘at risk’ patients (such as haemophiliacs).

In addition, the surveillance programme is identifying previously unrecognised prion diseases, such as VPSPr, that ‘do not fit well’ into the current classification. Clinically, people with VPSPr exhibit aphasia, ataxia, and parkinsonian signs, spongiform degeneration and vacuoles. The latter differ from the vacuoles of other common prion diseases. Furthermore,
VPSPr affects all three genotypes at codon 129 and seems to be the second ‘sporadic’ prion protein disease.\textsuperscript{14} VPSPr’s prevalence, relationship to sCJD and the risk to public health are yet to be determined.\textsuperscript{4}

Meanwhile, animals undergo intense surveillance to stop prions from entering the food chain. Cases in cattle peaked in 1992, when 36 680 animals were confirmed with BSE, and there has not been a case since 2009.\textsuperscript{18} However, surveillance for BSE in cattle, sheep, and goats revealed several newly discovered prion diseases including atypical scrapie in sheep, H- and L-type BSE in cattle and chronic wasting disease (CWD) in deer and elk. The ‘potential zoonotic risk to human health’ represented by these conditions ‘is hard to quantify’.\textsuperscript{4}

Thirty years after BSE’s identification, we have only just begun to scratch the surface of diseases caused by prions and we are a long way from a cure. Indeed, the more we look at prions the more conditions they seem to contribute to and the more important they become – underscored by their potential association with diabetes, Alzheimer’s and Parkinson’s disease. And, in reality, we do not yet know whether we have seen the last of vCJD. But one thing is clear: the importance of prion diseases goes far beyond a few mad cows.

References