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EDITORIALS

How widespread is variant Creutzfeldt-Jakob disease?

The disease seems rare but "infection" may be relatively common

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Variant Creutzfeldt-Jakob Disease (CJD) is the human form of bovine spongiform encephalopathy or "mad cow disease." It is one of the family of mainly neurodegenerative diseases known as spongiform encephalopathies because of their histological appearance. These diseases afflict animals and humans and are widely accepted as resulting from the toxic build-up of an aberrant form of a normal cellular protein, the prion protein. Bovine spongiform encephalopathy was common, with more than 36 000 cases in the peak year of the cattle epidemic in the United Kingdom (1992).[1] However, variant CJD has remained mercifully rare, with 177 cases in the UK to date (51 in the rest of the world, 27 of which were in France), and only one in the past two years.[2]

So, is variant CJD yesterday's news? The linked paper by Gill and colleagues (doi:10.1136/bmj.f5675) helps make clear why this is not the case.[3] Sporadic CJD, the "usual" form of CJD, was first described early last century and is found worldwide, with an annual incidence of around 1/1 000 000 population. Prion infectivity is notoriously difficult to inactivate and sporadic CJD had been shown to be transmissible by neurosurgery in case studies published as long ago as 1974. Transmission can also occur by injection or implantation of infected material derived from the central nervous system, as in the epidemic of CJD in recipients of human growth hormone derived from cadaveric pituitaries.[4]

In variant CJD, there are also concerns about spread from peripheral tissue and blood because disease related prion proteins have been demonstrated in lymphoreticular tissue.[5] Variant CJD has been transmitted by blood components and products from donors who later developed the disease, although a convincing case of transmission of variant CJD by surgery has not been documented.[6]

UK health agencies have taken several costly steps to secure the blood supply (leucodepletion of blood, exclusion of certain donors, and sourcing of blood products from outside the UK) and to reduce any risk of horizontal transmission by surgical instruments.[7] How necessary, or cost effective, these measures are depends mainly on how many people in the UK are "infected" with the variant CJD prion. Blood tests in specialist settings have been described,[8] but a test (ideally two tests) that could be used widely for diagnosis and screening remains elusive and would transform the approach to the problem.

In the absence of a blood test, anonymised population prevalence surveys using archived tissue from appendicectomies and tonsillectomies were carried out. Although abnormal prion protein was almost entirely absent from tonsils,[9] a previous survey of appendixes suggested a prevalence of 1/4000.[10] Gill and colleagues in their painstaking examination of more than 30 000 appendix samples arrive at a prevalence of 1/2000, the same order of magnitude. Unlike in clinical cases of variant CJD, no particular age group or geographical region was affected, and no susceptible genotype was identified. In the UK, patients with variant CJD have a modal age at death of 28 years and are diagnosed more often in the north of England and in Scotland. Confirmed cases have all been methionine homozygous (MM) at codon 129 of the gene encoding the prion protein (*PRNP*).[11] It is possible that abnormal deposition of prion protein in the appendix is simply a non-specific finding, so appendicectomy tissue from the 1970s and earlier, before bovine spongiform encephalopathy appeared, is being examined.

If "infection" with variant CJD prion proteins is common then precautionary measures are likely to be in place for a long time, and clinicians need to understand the logic behind them. Clinicians may encounter people deemed, in the words of UK public health agencies, to be "at increased risk" of CJD.[7] These are people who have received blood from someone with CJD or been operated on with surgical instruments that have been used on someone with CJD. The chance of these people having acquired the disease is thought to be great enough that they could, in turn, transmit the disease themselves. They are thus banned from donating blood and special arrangements need to be made for surgery that involves tissues in which prion proteins might be found. Advice from local public health or infection control teams should be sought. Local teams will also probably wish to seek more expert help, usually through the CJD Section of the National Centre for Infectious Disease Surveillance and Control of Public Health England that acts as a clearing house for queries and can link them with the UK's various specialist clinical and research teams.

Although we know much about these fascinating, if terrible, diseases, particularly at the protein chemistry and cellular level,

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many important questions remain. What is the disease phenotype and natural course of variant CJD in genotypes other than MM? What other animal prion diseases may be zoonotic? The replication mechanisms first seen in prion proteins have now been identified in other proteins involved in other common neurodegenerative diseases, including Aβ, amyloid-β in Alzheimer's disease, α-synuclein in Parkinson's disease, and tau in several different conditions.[12] How often, if ever, are any of these transmissible? The UK's prion research capacity with expertise in human and veterinary disease surveillance and pathology, as well as animal facilities for transmission experiments, is well placed to answer such questions. Further disinvestment would be premature.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: From 2007 until its dissolution in 2011, I was a member of the UK's Spongiform Encephalopathy Advisory Committee (SEAC) and I have been a member since 2011 of the Advisory Committee on Dangerous Pathogens. Both these independent scientific advisory groups took an active interest in this work and encouraged the UK government to fund work on the prevalence of spongiform encephalopathies.

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