2013-10-26-076 Prion disease update 2013 (01)
To: (01) Public health and One Health Initiative; (07) Zoonoses, general;

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Subject: PRO/AH/EDR> Prion disease update 2013 (01)

PRION DISEASE UPDATE 2013 (01)
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A ProMED-mail post

[1]
Date: Mon 14 Oct 2013
Source: British Medial Journal [edited]
<http://www.bmj.com/press-releases/2013/10/14/researchers-estimate-one-2000-people-uk-carry-variant-cjd-proteins>

Around one in 2000 people in the UK may carry variant CJD proteins, concludes a large scale survey published in BMJ.com today [14 Oct 2013; [By Sebastian Brandner, professor of neuropathology, Division of Neuropathology, the National Hospital for Neurology and Neurosurgery, and Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK <s.brandner@ucl.ac.uk>.].

The survey provides the most robust prevalence measure to date and identifies abnormal prion protein across a wider age group than found previously and in all genotypes. An accompanying editorial says that although the disease remains rare, "infection" may be relatively common, and doctors need to understand the public health measures that are in place to protect patients.

Variant Creutzfeldt-Jakob disease (vCJD) is a degenerative brain disease often called the human form of bovine spongiform encephalopathy (BSE) or "mad cow disease." It emerged after widespread exposure to BSE prions in the late 1980s and early 1990s through contaminated meat products in the food chain. Although there have been only 177 clinical cases of vCJD to date in the UK, previous studies have estimated that around one in 4000 people may carry vCJD prions.
But uncertainty remains about how many people will eventually develop the disease. And it is still not clear what risk carriers pose of transmitting the disease by blood transfusion or surgery. Despite this, UK health agencies have already taken steps to secure the blood supply and reduce any risk of transmission by surgical instruments.

A team of UK researchers decided to conduct a further survey to better understand how many people in the UK may be carriers and to identify their genetic make-up (genotype). They examined over 32 000 anonymous appendix samples from people of all ages who had their appendix removed between 2000 and 2012 at over 41 hospitals across England. Of these, 16 samples were positive for abnormal prion protein, indicating an overall prevalence of 493 per million population. From this figure, the research team estimated that one in 2000 people are likely to be carriers.

The presence of prion protein in those born in 1941-60 did not differ significantly from those born between 1961 and 1985 and was similar in both sexes. And when the samples were grouped into 3 broad geographical areas (northeast and northwest; southeast coast, southwest, and London, and East and West Midlands), there were no apparent differences in abnormal prion prevalence. As well as finding no particular age group or geographic region affected, no susceptible genotype of patients was identified.

Genetic testing of the 16 positive samples revealed a higher proportion of valine homozygous (VV) genotype in codon 129 of the gene encoding the prion protein (PRNP) compared with the general UK population. This also differs from the 177 patients with vCJD, all of whom to date have been methionine homozygous (MM) genotype. The concern is that individuals with this VV genotype may be susceptible to developing the condition over longer incubation periods, or they may not show any clinical signs of disease, say the authors. They stress that the number of patients with clinical vCJD is still well below the number suggested by the prevalence of abnormal prion protein, even for those who carry the MM genotype. Nevertheless, they say it is essential to continue research into tests to detect

abnormal prion protein in blood and to examine tissue from the 1970s and earlier, before BSE appeared.

In an accompanying editorial [see below], Roland Salmon, a retired consultant epidemiologist, says that although we know much about these fascinating, if terrible, diseases, many important questions remain about their characteristics and what other animal prion diseases may be transmitted to humans. He argues that the UK's prion research capacity "is well placed to answer such questions" and that "further disinvestment would be premature."

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[2]
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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). 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 2 years.

So, is variant CJD yesterday's news? The paper by Gill and colleagues [Part 1 above] helps make clear why this is not the case. Sporadic CJD, the "usual" form of CJD, was 1st 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.

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. 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.

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. 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, but a test (ideally 2 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, a previous survey of appendixes suggested a prevalence of 1/4000. 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). 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. These are people who have received blood from someone with CJD or who have been operated upon 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 to 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, 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 1st seen in prion proteins have now been identified in other proteins involved in other common neurodegenerative diseases, including AB, amyloid-B in Alzheimer's disease, a-synuclein in Parkinson's disease, and tau in several different conditions. 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.
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Communicated by:
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[see also:
Creutzfeldt-Jacob disease - Ireland: transmission risk
20130720.1834907
2012

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