Image: © vege – Fotolia.com

Potential Prognosis

As long as there is a lack of early-stage, ante-mortem diagnostic tools available for variant Creutzfelt-Jakob disease, the number of those suffering with the initial prion infection will remain unknown. With so much uncertainty surrounding its causes – and myriad ethical dilemmas – what does the future hold for patients?

Shelley Bowers,
EPC Industry Advisor

A recent report on the CBS News website highlighting newly-diagnosed cases of bovine spongiform encephalitis (BSE) in Alberta, Canada, will no doubt reignite the debate about how safe it is to consume beef (1). It is well-recognised that prions – the misfolded proteins, known as PrP-Sc, that cause BSE in cows – are the most likely cause of variant Creutzfelt-Jakob disease (vCJD) in humans (2). How they cause the disease is still debated, with current theories suggesting that an accumulation of prions in a nerve cell results in its injury and death. Others believe that the transformation of PrP-C to PrP-Sc leads to the neurodegenerative condition (2).

This highly tenacious and unique life form, due to its lack of genetic material, is now thought to have been transmitted into the human population through the consumption of infected beef – with epidemiological data pointing to a strong correlation between the two (2).

Possibly Widespread?

Once infection occurs, there can be a latency period of anything up to 50 years before the neurodegenerative symptoms, created by the prions, start to appear. This means the number of potential vCJD carriers in the UK is unknown at present, but could be large (3).

Indeed, in 2011, the high-profile death of Holly Mills in the UK served as a reminder that the disease is as deadly and elusive to detect today as it has been since the first recorded cases appeared in humans in early 1996 (4).

In fact, a world authority in prion research, Professor Graham Jackson from the Medical Research Council Prion Unit at University College London, said in an article on vCJD: "This problem has not gone away – far from it" (5). And it is something we should all be concerned about – especially as

the same report details recent research that shows there may be as many as 1 in 2,000 people in the UK carrying the infection, but who are currently subclinical (5). This means there could soon be a large number of patients needing a reliable diagnostic test, if vCJD is a suspected cause of their symptoms.

The lack of knowledge regarding the level of infection with prions in the UK population creates another important issue: accidental iatrogenic transmission. This raises the possibility of vCJD being passed on via tissue and organ grafts, blood products and transfusions, and contaminated medical instruments (6,7).

Some researchers even suggest that the majority of new cases will be via diseased blood products, rather than through the primary route of eating infected meat (8). And, according to an article by the MRC Prion Unit, there are "several thousand patients known to have received contaminated blood products who are considered to be at risk" (8).

This being the case, and with no cure available – nor looking like it is on the horizon any time soon – it is imperative that a reliable, early-stage diagnostic tool – preferably one that can identify carriers before symptoms emerge – is developed (2,8). Not only to find the true prevalence of vCJD in the UK, but also to identify those that need to be referred for care and to prevent any further cross-infection via iatrogenic transmission.

Current Diagnostic Testing

At present, it is only possible to definitively diagnose vCJD post-mortem by examining the brain pathology, usually in the form of a brain biopsy (2). These tests look for the typical vCJD biomarkers in the brain tissue, and include using western immunoblot and/or immunochemistry to detect prion deposition and accumulation. Other changes indicating the presence of infection could be nerve cell loss, vacuolation and gliosis (2). Brain biopsies are used ante-mortem too, but this is rare as the risk to the patient and the medical team performing the procedure is very high (9). There have even been reports of medical staff refusing to deal with patients suspected of carrying the disease, because of the risk of prion infection (10).

Another ante-mortem test includes diffusion-weighted imaging, as part of a magnetic resonance imaging sequence. This method has proven to be a valuable addition to the vCJD diagnostic toolbox, and it aims to find evidence of a bilaterally-increased pulvinar signal, which is present in approximately 75% of infected patients (11). As this signal is highly vCJD-specific, it can be used as an indicator of disease presence (2).

An electroencephalogram may also be used as part of the diagnostic process (9). However, its primary function is as a tool to diagnose sporadic CJD – not the variant form – so its usefulness is questionable. The changes that occur in 'classic' CJD are often absent in vCJD patients, or are only present in the very late disease stages (12).

Lumbar puncture is another of the currently used, but largely ineffective, diagnostic tools. It is used successfully to diagnose sporadic CJD, as a positive diagnosis of this form of neurodegeneration reveals elevated levels of 14-3-3, t-tau, S100 and neuron-specific enolase protein biomarkers in the cerebral fluid (CSF) (2). The CSF can also be tested for the biomarkers of other problems, such as infection or inflammation of the brain, that may be causing the presenting symptoms (9,13). This mode of diagnosis is more of an elimination process, in that sporadic CJD, and a number of other possible causes, will have been ruled out.

Tonsil biopsies – although being highly effective at diagnosing vCJD through positive identification of the abnormal PrP-Sc protein in the tissue – have fallen out of favour in recent years. This is largely due to the invasive nature and associated risks of the procedure, combined with a lack of effective treatment to administer, should a positive diagnosis be found (9,14).

Reliability Issues

As is evident, the issues with the current diagnostic methods are widespread and varied – this article being too brief to even approach those associated with false-positive and false-negative diagnoses.

A further important concern with the reliability of current diagnostic tests is that the number of prions needed to create vCJD symptoms differs depending on the prion strain, the type of prion disease and the inoculation route – with direct intracerebral inoculation being the most effective method (2). This makes the setting of testing parameters particularly difficult and long-winded.

However, one of the biggest stumbling blocks to all these diagnostic techniques is that they only identify patients very late in disease progression. Often, diagnosis does not take place until patients are approximately two-thirds of the way though the natural progression of the disease, or when they have already succumbed to the destructive effects. So, sadly, even if a positive diagnosis is revealed, any potential treatments at this advanced stage would prove unsuccessful as too much degeneration will have already taken place (2).

This highlights the need for a diagnostic tool that will enable early detection of vCJD, so that when an effective treatment is discovered, it can be administered early enough to prevent the neurodegenerative symptoms occurring in the first place.

Recent Techniques

Despite the fact that the necessary early detection techniques have still not been discovered, there are some promising developments. These new tests are important because they represent a step forward in accurate ante-mortem diagnosis.

The first is nasal testing – developed by the National Institutes of Health and Italian scientists – which uses a brush to collect olfactory neurons connected to the brain (15). A rigid fibre-optic rhinoscope is inserted into the nasal cavity of the patient and, alongside this, a brush is inserted and gently rolled over the surface, collecting the neurons as it sweeps past the mucosal lining (15).

The researchers studied samples of nasal tissue from 74 participants – 31 with confirmed CJD, and 43 presenting symptoms of other neurodegenerative diseases or no known disease. The investigators were able to identify 97% of those infected with CJD – the test can be used for all types – and 100% of those with no CJD (15). Validation of the method is ongoing, but the research team are confident and continue to work on simpler swabbing collection techniques for samples. However, as has already been mentioned, the test is only for later-stage patients, who are already displaying symptoms.

Another new development in the identification of vCJD involves a blood test. The idea of using this type of test to check for prion infection has been in the pipeline for a while. But, with the numbers of misfolded PrP-Sc prions extremely low in the blood, as well as being virtually indistinguishable from normal proteins, it has remained elusive (7). The first promising results came in March 2011 from the Medical Research Council, when it announced the development of a prototype blood test for vCJD, but only in symptomatic patients (6). This prompted further research, resulting in another announcement in mid-January 2014, confirming that an accurate blood test for prions had been developed (7,16).

Crucially, as with the nasal brush technique, the blood test is primarily only for patients who are already displaying symptoms. Its usefulness in sub- and preclinical patients remains in question (16). Still, researchers are confident enough in the technique to suggest its use in wide-scale testing for vCJD, involving 20,000 participants each from prion- and non-prion-exposed groups (6). The data collected from this study could be used to determine the necessity of routine testing of blood, organ and tissue donations, and when patients are required to undergo high-risk surgical procedures (16).

Ethical Problems

Before we get to that stage though, there are some thorny ethical issues connected to wide-scale testing of the population that must be tackled. In particular, the question of what happens to participants who test positive? Will they be informed of their status and, if so, how will the issue be addressed? The problem is that there are far more people infected with vCJD prions than there are presenting the effects of them and, as of now, scientists are not yet 100% sure why some people develop symptoms while others do not (17). There is research that suggests the development of symptoms is related to the multiple myeloma gene, which is carried by about 40% of the population, with all diagnosed cases at that point being in this gene group (11). However, that was called into question in 2009, when it emerged that a patient with malformed vertebrae genes had died from vCJD (11).

This means informing people with a positive diagnosis will be tricky, as the patient will then be told there is no cure and that the disease is, invariably, fatal. Should sufferers simply be told: "You have all the makings of a fatal neurodegenerative disease, but you may or may not develop symptoms over the next few years"? Obviously, this is not an ideal situation.

In a similar scenario, the discovery of BRCA1 and BRCA2 genes – which have been implicated in increasing the chances of developing breast cancer by 80-90%, in both men and women – sparked panic in the population (18).

As the media covered the finding of the so-called 'breast cancer gene', it prompted a number of high-profile women – most notably Angelina Jolie – to have preventative double mastectomy surgery (19). Jolie has since gone on to have a salpingo-oophorectomy, as the gene also increases the

chances of developing ovarian or fallopian cancer by up to 50% (20). Many other women followed their examples and opted to have this hugely invasive, but largely preventative, surgery (21).

However, unlike breast cancer, there are no preventative treatments or procedures for vCJD; there is nothing the individual can do about it, even if they know. This may lead to feelings of depression, as sufferers contemplate their future, knowing that they may develop a fatal neurodegenerative disease that is entirely beyond their control. Research shows that giving a positive fatal diagnosis to a patient can create permanent feelings of anxiety, leading to a whole raft of other issues. Some people may prefer not to know until symptoms start to occur (22).

Unnecessary Worry?

Any decision to test humans on a large scale should also take into account the fact that many people carry prions, but do not ever develop the symptoms. This could mean that many of those diagnosed as being prion-positive may worry about the onset of symptoms unnecessarily. And, as already mentioned, the psychological ramifications of being given a potentially fatal diagnosis are likely to be huge – with known effects including denial; anger at family, friends and carers; decrease in faith and belief; and withdrawal. Suffering from any or all of these symptoms can cause severe problems with personal and professional relationships (23).

With the probability of 1 in 2,000 people at risk of developing vCJD in the UK, the potential for a large number of individuals living with debilitating psychological problems is large. These issues could cause untold damage to patient quality of life – damage that could be for nothing if the symptoms never develop.

These, and many other concerns, need careful consideration before any large-scale testing can take place (2). This is regardless of whether it is done anonymously – which raises its own set of ethical issues too broad to cover here – or with patient identification.

Future Pursuits

It appears that, without effective treatments readily available, early diagnosis will only serve to prevent accidental transmission of vCJD iatrogenically, and inform and prepare the patient and their family for what is to come. Which is, of course, a wholly worthwhile pursuit – but, sadly, at the present time, it will not help with prevention or disease treatment.

However, there are reasons to be positive for the future. It is hugely encouraging to have two reliable, non-invasive, ante-mortem diagnostic tools to work with. Hopefully, these discoveries mark the start of untangling the prion problem, and early diagnosis and treatment will soon be something we all have access to.

References

1. Visit: www.cjad.com/cjad-news/2015/02/13/agriculture-minister-says-alberta-mad-cow-case-wont-affect-beef-trade
2. Visit: www.ncbi.nlm.nih.gov/pmc/articles/pmc3818451
3. Visit: www.prion.ucl.ac.uk/clinic-services/research/new-tests-for-prion-disease
4. Visit: www.who.int/mediacentre/factsheets/fs180/en
5. Visit: www.nature.com/news/one-in-2-000-uk-people-might-carry-vcjd-proteins-1.13962
6. Visit: www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)62308-2/abstract
7. Visit: www.ncbi.nlm.nih.gov/pmc/articles/pmc3894497
8. Visit: www.prion.ucl.ac.uk/research/mrc-research-groups/molecular-diagnosis
9. Visit: www.bseinfo.org/vcjddiagnosis.aspx
10. Visit: www.medicinenet.com/creutzfeldt-jakob_disease/page5.htm#how_is_cjd_transmitted
11. Visit: www.cdc.gov/ncidod/dvrd/vcjd
12. Brown P, Brandel JP, Preese M and Sato T, Iatrogenic Creutzfeldt-Jakob disease: The waning of an era, *Neurol* 67: pp389-393, 2006
13. Hueston W and Bryant CM, Transmissible spongiform encephalopathies, *J Food Sci* 70: pp77-87, 2005
14. Hoshi K *et al*, Creutzfeldt-Jakob disease associated with cardavericdura mater grafts in Japan, *Neurol* 55: pp718-721, 2000
15. Visit: www.nih.gov/news/health/aug2014/niaid-06.htm
16. Visit: www.prion.ucl.ac.uk/press-media/press-releases/blood-test-for-vcjd
17. Visit: www.prionalliance.org/2013/12/02/what-are-human-prion-diseases
18. Visit: www.cancerresearchuk.org/about-cancer/type/breast-cancer/about/risks/breast-cancer-genes
19. Visit: www.edition.cnn.com/2013/05/14/showbiz/angelina-jolie-double-mastectomy
20. Visit: www.nytimes.com/2015/03/24/opinion/angelina-jolie-pitt-diary-of-a-surgery.html
21. Visit: www.wtsp.com/story/news/local/2013/05/14/jolie-not-alone-in-decision-for-double-mastectomy/2022572
22. Visit: www.nhs.uk/conditions/predictive-genetic-tests-cancer/pages/introduction.aspx
23. Visit: www.uptodate.com/contents/psychosocial-issues-in-advanced-illness

About the author

Shelley Bowers is an experienced writer in the areas of law, publishing and medicine – both allopathic and complementary – as well as an Industry Advisor for *EPC*. Educated to BSc level, she has a keen interest in the technological advances of the modern world of medicine, with a particular focus on how they impact upon, and interact with, both the patient and the wider environment.
Email: shelleybowers609@gmail.com