Transmissible Spongiform Encephalopathies:

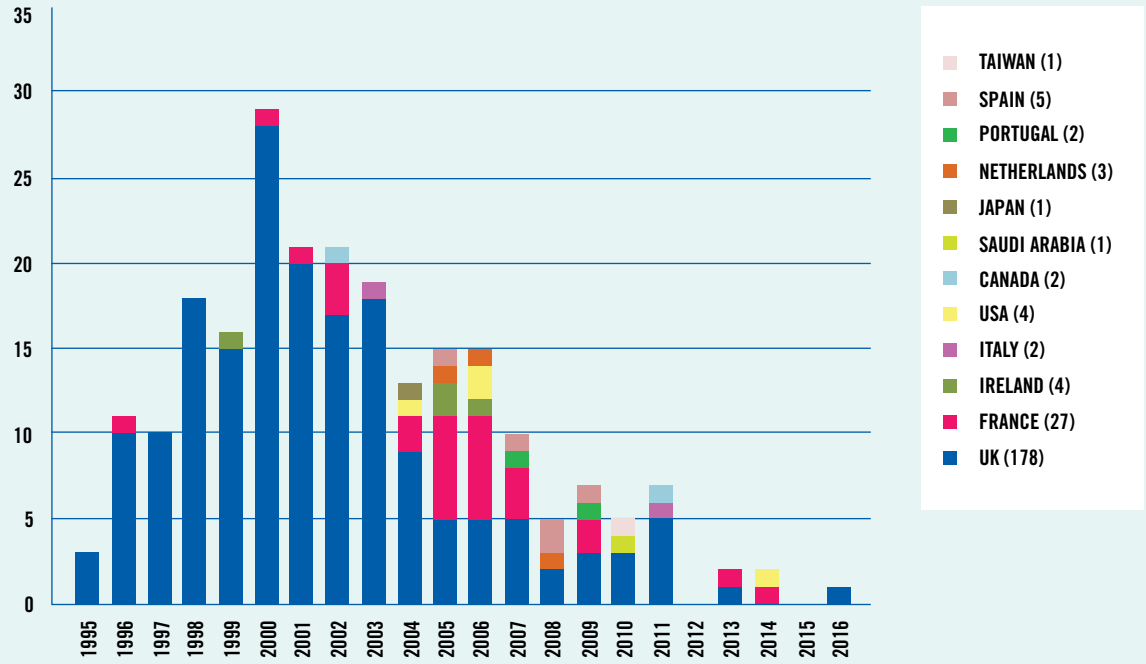
PAST, PRESENT, AND FUTURE

BY LARISA CERVENAKOVA, M.D., PH.D, PPTA MEDICAL DIRECTOR

The first issue of The Source magazine, released in September 2001, was dedicated almost entirely to transmissible spongiform encephalopathies (TSEs)/prion diseases, and their possible iatrogenic human-to-human transmission through blood and blood-derived therapeutic treatments. Special attention was given to variant Creutzfeldt-Jakob diseases (vCJD), the rare form of human TSE mainly occurring in the UK and linked to dietary exposure to products contaminated with prion isolate of bovine spongiform encephalopathy (BSE), known to the public as "mad cow" disease.[1] In the same year, the National CJD Research and Surveillance Unit in the UK reported, for the first time, a lower number of vCJD cases than in previous years since the first patients were diagnosed in 1995 (**Figure 1**).[2] At that time, no one could predict whether the declining trend in number of vCJD cases signaled a turning point in the epidemic, considering the enormous extent of the BSE epidemic and the probability of significant human exposure to the agent. An additional uncertainty surrounded the incubation period of TSE, which could vary from 4-20 years and in some cases can even exceed 50 years, as had been reported for patients afflicted with kuru—an almost-extinct condition in Fore people of Papua New Guinea who were infected through practicing cannibalistic rituals.[3,4] Long incubation periods had also been described in iatrogenic CJD patients to whom the disease was accidentally transmitted through treatment with prion contaminated pituitary-derived human growth hormone, or gonadotropin or dura mater transplant.[5] Especially worrisome was the fact that vCJD affected younger individuals (the youngest patient was 12 years old) with a mean age at onset of 28 years. In contrast, sporadic CJD (sCJD) patients, afflicted with the most common form of TSE, develop the disease at significantly older age—in their '60s.

We needed to know what the future would hold and how we should prepare for the situation described by one epidemiological predictive model that provided the possibility of an epidemic affecting between one thousand and more than twenty thousand individuals in the UK alone.[6] It was a time of uncertainty, in which the question of whether there were prions present in the blood of vCJD-afflicted individuals and in blood of healthy people who might be silently incubating the disease had yet not been answered. Since then, PPTA has repeatedly returned to the issue of prions in number of subsequent publications addressing human and animal TSEs, including BSE, vCJD, and sCJD. The most recent articles mentioning

Figure 1: vCJD Cases Worldwide



these conditions were published in the 2012 summer issue of The Source and included interviews with Jay Epstein, M.D. of the Center for Biologics Evaluation and Research, FDA and Glenda Silvester, Ph.D. of the Human Medicines Development and Evaluation Unit, EMA.[7] By that time, complex issues had been addressed at regulatory and research levels, and many global decisions were proven to be justifiable in preventing a wide spread of vCJD epidemic. Coincidentally, since 2012 only two new cases of vCJD were diagnosed in the UK (as of Dec. 5, 2016), and two new vCJD patients were reported in France—the country with the next highest number of cases,[8] and one new case was identified in the U.S. with strong evidence of possible exposure to BSE outside the country (**Figure 1**).[9]

From the time when the first four individuals died from vCJD in the UK in 1995, in total, 178 people in the UK, 27 people in France, and more than two dozen people around the world—mostly in European countries—were lost due to the same condition (**Figure 1**). Regrettably, we witnessed the probable transfusion transmissions of vCJD to four individuals in the UK who received non-leukoreduced red blood cell concentrates from three donors in the pre-symptomatic phase of the disease.[10] The universal leukoreduction of blood and blood components was implemented in the UK, France, Canada, and many other European countries by the end of 1999 and in Germany in October 2001 to reduce the possibility of vCJD transmission through the white blood cells, which were identified at the time as the probable primary source of infection in blood.[11] In the United States, the universal leukoreduction has been recommended to the blood establishments by the FDA Blood Products Advisory Committee and the Advisory Committee on Blood Safety and Availability in 1998 and 2001, respectively. The issue of whether this preventive measure alone was sufficient to eliminate the risks of vCJD transmission through blood transfusion is still open for discussion but, as of today, no vCJD cases related to transfusion of leukoreduced therapeutics have been identified.

In one person with hemophilia who died at the age of 73, the main diagnostic marker of TSEs, the misfolded disease-associated prion protein (PrPTSE), was found in one sample of many prepared from the spleen during retrospective pathological study.[12] This individual died from a non-neurological disease and there was no evidence of PrPTSE or pathological changes consistent with TSE in the brain—the main organ suffering from the consequences of the infection. The patient was heterozygous at a codon 129 methionine/valine (M/V) of the prion protein gene (PRNP), whereas almost all other vCJD patients had been methionine/methionine (M/M) homozygous at codon 129. The exceptions were reported in a recent vCJD patient who died in 2016 and in one of the four recipients of non-leukoreduced red blood cells, mentioned above, both had a PRNP codon 129 M/V profile. This latter person never developed clinical signs of neurological disease but the presence of PrPTSE was found in the patient's spleen and one lymph node.[13] The codon 129 PRNP genotype has been shown to influence the incubation period and duration of the disease, as well as clinical and neuropathological features of TSEs and even biochemical prion protein characteristics. The PRNP codon 129 M/V vCJD cases deserve special attention

because of the retrospective study of appendix samples collected between 2000-2012 that was undertaken in the UK.[14] The presence of PrPTSE was found in 16 out of 32,441 examined samples, yielding the estimate of approximately one in two thousand individuals potentially silently incubating vCJD. All three PRNP codon 129 genotypes (M/M, M/V, and V/V [valine/valine]) were represented within this group of sixteen samples, an indication that a person with any PRNP codon 129 genetic makeup can be susceptible to vCJD infection. The question now is whether the comparatively long incubation periods associated with a codon 129 M/V PRNP genotype, coupled with the estimated frequencies of silent vCJD infection, could contribute to a possible future reoccurrence of vCJD cases.

Regardless of the outcome, we can state that multiple preventive mandatory and regulatory measures put in place by government agencies have been extremely important in safeguarding plasma-derived and recombinant therapeutics from contamination with vCJD and other human TSE agents. In addition, the industry has been highly responsive to the threats of the vCJD epidemic and has carried out numerous studies to assess the clearance of prions during the manufacturing processes, as well as introduced industrywide additional steps for prion removal.[15]

Sporadic CJD, is believed to occur spontaneously without any known link to relevant environmental or iatrogenic exposure. More than 20 years of epidemiological follow-up observations conducted by the American Red Cross provide no evidence of sCJD transmission through blood transfusion.[16] The Transfusion Medicine Epidemiology Review study that was initiated in the UK in 1997 and still continues, also reports no evidence of transfusion transmission of sCJD.[17]

In conclusion, the years of commitment and investment in research supported by an extensive record of publications and presentations at various scientific meetings documented the seriousness with which the industry addresses issues of patient safety. We hope that there will be no unexpected surprises stemming from transmission of zoonotic TSEs to humans, one of which—chronic wasting disease (CWD) of cervids—has not only spread through the North American continent affecting deer, elk, and moose, but also reached South Korea through commercially exported farmed animals. In the past year, CWD was first found in wild reindeer during the tagging and registration,[18] and later in two additional reindeer and two moose by targeted surveillance in Norway (as of December 2016).[19] Presently, we have no epidemiological evidence that CWD has ever infected humans, but as always, only continuing vigilance will ensure that no preventable human tragedies related to TSEs will occur in near future.

Acknowledgment: I am grateful to Jan M. Bult and Dr. Paul Brown for helpful comments on the manuscript. ●

References:

1. The Source, September, 2001, pp.3-16.
2. Will RG, Ironside JW, Zeidler M, Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet. 1996; 347:921-5.
3. Cervenáková L, Goldfarb LG, Garruto R, Lee HS, Gajdusek DC, Brown P. Phenotype-genotype studies in kuru: implications for new variant Creutzfeldt-Jakob disease. Proc Natl Acad Sci U S A. 1998;95:13239-41.
4. Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, Alpers MP. Kuru in the 21st century - an acquired human prion disease with very long incubation periods. Lancet. 2006;367:2068-74.
5. Brown P, Brandel JP, Sato T, Nakamura Y, MacKenzie J, Will RG, Ladogana A, Pocchiari M, Leschek EW, Schonberger LB. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis. 2012;18:901-7. doi: 10.3201/eid1806.120116.
6. Ghani AC, Donnelly CA, Ferguson NM, Anderson RM. Assessment of the prevalence of vCJD through testing tonsils and appendices for abnormal prion protein. Proc Biol Sci. 2000;267:23-9.
7. The Source, Summer 2012, pp. 20-23.
8. http://www.eurocjd.ed.ac.uk/surveillance data 1.html
9. Maheshwari A, Fischer M, Gambetti P, Parker A, Ram A, Soto C, Concha-Marambio L, Cohen Y, Belay ED, Maddox RA, Mead S, Goodman C, Kass JS, Schonberger LB, Hussein HM. Recent US Case of Variant Creutzfeldt-Jakob Disease-Global Implications. Emerg Infect Dis. 2015;21:750-9. doi: 10.3201/eid2105.142017.
10. Checchi M, Hewitt PE, Bennett P, Ward HJ, Will RG, Mackenzie JM, Sinka K. Ten-year follow-up of two cohorts with an increased risk of variant CJD: donors to individuals who later developed variant CJD and other recipients of these at-risk donors. Vox Sang. 2016;111:325-332. doi: 10.1111/vox.12426.
11. Bassuni WY, Blajchman MA, Al-Moshary MA. Why implement universal leukoreduction? Hematol Oncol Stem Cell Ther. 2008;1:106-23.
12. Peden A, McCardle L, Head MW, Love S, Ward HJ, Cousens SN, Keeling DM, Millar CM, Hill FG, Ironside JW. Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. Haemophilia. 2010;16: 296-304. doi: 10.1111/j.1365-2516.2009.02181.x. Epub 2010 Jan 12.
13. Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. Lancet. 2004;364: 527-9.
14. Gill ON, Spencer Y, Richard-Loendt A, Kelly C, Dabaghian R, Boyes L, Linehan J, Simmons M, Webb P, Bellerby P, Andrews N, Hilton DA, Ironside JW, Beck J, Poulter M, Mead S, Brandner S. Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey. BMJ. 2013;347:f5675. doi: 10.1136/bmj.f5675.
15. Cai K, Gröner A, Dichtelmüller HO, Fabbrizzi F, Flechsig E, Gajardo R, von Hoegen I, Jorquera JI, Kempf C, Kreil TR, Lee DC, Moscardini M, Pölsler G, Roth NJ. Prion removal capacity of plasma protein manufacturing processes: a data collection from PPTA member companies. Transfusion. 2013;53:1894-905. doi: 10.1111/trf.12050.
16. Dorsey K, Zou S, Schonberger KB, Sullivan M, Kessler D, Notari E 4th, Fang CT, Dodd RY. Lack of evidence of transfusion transmission of Creutzfeldt-Jakob disease in a US surveillance study. Transfusion 2009;49:977-84. Epub 2009 Jan 5.
17. Urwin PJM, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review. Vox Sanqunis 2016;110:310-316.
18. Benestad SL, Mitchell G, Simmons M, Ytrehus B, Vikøren T. First case of chronic wasting disease in Europe in a Norwegian free-ranging reindeer. Vet Res. 2016;47:88. Doi: 10.1186/s13567-016-0375-4.
19. https://www.bds.org.uk/index.php/documents/125-cwd-update-from-norway-dec-16/file