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Case Report

From BSE Man-Made Disaster to vCJD Epidemic Risk: A Look Back and a Look Forward: The Need to Translate the Scientific Complexity and Uncertainty into Effective Policy-Making Decisions

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Abstract

Bovine spongiform encephalopathy (BSE), described for the first time in 1987, in the United Kingdom (UK), is a transmissible spongiform encephalopathy (TSE) of cattle. Prion diseases or TSEs are a family of lethal, neurodegenerative disorders including Creutzfeldt-Jakob disease (CJD) in humans, scrapie in sheep and goats and chronic wasting disease (CWD) in deer and elk. Epidemiologic data together with experimental scientific evidence established the causal link between BSE and the "variant form" of CJD (vCJD), and the human risk associated to the consumption of meat products contaminated by the BSE infectious agent. Because of its association with vCJD, BSE became the most challenging and burdensome in terms of economic resources, worldwide, infectious disease in the last 20 years impacting on trade, and importantly on public health issues related to food and feed safety. To date, just remain alarmist uncertainties about the future number of vCJD cases, also possibly linked to secondary transmission from sub clinically infected people by way of medical treatments involving the use of vCJD-contaminated blood products.

Transmissible spongiform encephalopathies (TSE), or prion diseases, are a family of lethal, neurodegenerative disorders including Creutzfeldt-Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE), also known as mad cow disease, in cattle, scrapie in sheep and goats and chronic wasting disease (CWD) in deer and elk [1,2]. Prions are peculiar pathogens, composed mostly, if not entirely, of a host-encoded protein (i.e., cellular prion protein or PrP^{C}) misfolded in a partially protease-resistant, aggregated form, named PrP^{TSE} that accumulates mainly in central nervous system (CNS) of affected individuals [3,4].

Interestingly, prions are apparently devoid of coding nucleic acids and largely resistant to common chemical and physical cleaning and disinfection [5]. To date, no therapeutic intervention in man showed effective results in spite several compounds displayed antiprion activity in preclinical experimental studies [6,7].

TSE have an incubation period remarkably long, in cattle on average of five years and in humans, in some cases, exceeding decades. BSE was described for the first time in 1987, in the United Kingdom (UK), as a new disease in cattle [8-10]. BSE peaked in January 1993 at almost 1,000 new cases per week. The origin of the disease was most likely from feeding cattle meat and bone meal (MBM) derived from an infected cow that developed the disease spontaneously. Certainly, outbreak was then amplified all by feeding MBM prepared from cattle to young calves. Oral exposure experimental studies showed that very small amounts of BSE infected brain (*i.e.*, as little as 0.1 g, and probably 0.01 g) were enough to infect cattle orally [11]. Thus, the basic preventive measure against TSE was the feed ban: a ban on the use of processed animal protein (PAP) in feed for ruminants (*i.e.*, cattle, sheep and goats) was introduced in July 1994. The ban was expanded in January 2001 with the feeding of all PAP to all farmed animals being prohibited, with certain

limited exceptions, to be able to minimize cross-contamination between feed containing PAP intended for species other than ruminants and feed intended for ruminants. Only certain animal proteins considered to be safe (*i.e.*, fishmeal) could be used, and even then under very strict conditions [12,13].

Ten years after the first description of BSE, in the UK, a new fatal neurodegenerative disease, resembling CJD (at first described in 1920), was reported in ten human cases [14]. Epidemiologic data together with experimental scientific evidence established the causal link between BSE and the *"variant form"* of CJD (vCJD), and the human risk associated to the consumption of meat products contaminated by the BSE infectious agent [15,16]. In BSE-infected cows, infectious agent replicates and accumulates in specific organs (*i.e.*, brain, spinal cord, tonsils, distal ileum, dorsal root ganglia, trigeminal ganglia and eyes), all together referred to as *specified risk materials* (SRM). Under the provisions of European Regulation (EC) No 999/2001 ("*the TSE Regulation*") to protect public health, these tissues were at once banned from entering the human food chain in all European Union Member States and providing for their definitive elimination at source [12].

Because of its association with vCJD, BSE became the most challenging and burdensome in terms of economic resources, worldwide, infectious disease in the last 20 years. Thus, BSE, as emerging anthropozoonotic disease [*i.e., an animal disease (zoonosis) maintained in nature by animals and transmissible to humans (e.g. rabies or brucellosis)*], impacted for a significant long time on economics, trade, and also on public health issues related to food and feed safety. Every tentative extrapolation from "*conventional*" food borne epidemics to epidemics of BSE and vCJD would appear clearly superficial [17].

Finally, BSE affected more than 180,000 cattle only in UK and about 7,000 cattle worldwide [visit the BSE portal on the World Organisation for Animal Health (OIE) website: <*http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/*>]. But according some initial estimates millions of cattle meat entered the table of consumers making theoretically possible that thousands asymptomatic but infected persons could develop the disease during their life. Fortunately, and i*n contrast* with this *apocalyptic scenario* from October 1996 to January 2016, 177 cases of vCJD were just reported in the United Kingdom (<<*http://www.cjd.ed.ac.uk/documents/figs.pdf*>> - as at 5th January 2016), and 52 cases in other countries [*i.e.*, 27 from France, 5 from Spain, 4 from Ireland, 4 from the United States, 3from the Netherlands, 2 from Portugal, Italy and Canada and one each from Japan, Saudi Arabia, Taiwan (<*http://www.cjd.ed.ac.uk/documents/worldfigs.pdf;* updated 29/04/2015*);* two of the four U.S. cases, two of the four cases from Ireland, one of the two cases from Canada, and the single case from Japan were likely exposed to the BSE infectious agent while residing in the United Kingdom; the third and the fourth US patients, born outside the Americas were likely infected before they moved to the United States].

In contrast to the sporadic form of CJD, vCJD affected younger patients: the median age at onset of disease was 26 years and the median age at death 28 years compared with 67 years for the median age at onset and 68 years for the median age at death for sCJD. The youngest vCJD case was aged 12 years at onset while the oldest case was aged 74 years. The median duration of illness from the onset of first symptoms to death was 14 months compared with a median duration of illness for cases of sCJD of 4 months during the period 1990-2014 (<*http://www.cjd.ed.ac.uk/documents/report23.pdf* >).

Following the successful containment of the BSE epidemic in cattle, the incidence of vCJD in the United Kingdom has declined since 2000, peaking with 28 deaths per year to a current incidence of about 1 to 2 diagnoses/death per year, but expecting a long tail end of the epidemic curve.

Importantly, vCJD is transmitted through blood or blood derivatives, even from subclinical donors. In this context, since 1999, the United Kingdom has no longer sourced plasma from its inhabitants, and as a further precautionary measure against the occurrence of vCJD, provided leukocyte depletion (removal of white blood cells) from blood transfusions. Hence, several countries have also prohibited blood donations from those have traveled or resided in countries with higher risk of BSE for a cumulative period of 3 or more months between 1980 and the end of 1996. To date, four instances (3 clinical cases of vCJD and one asymptomatic recipient post-mortem confirmed for the presence of abnormal prion protein deposition in the spleen) of probable transfusion transmitted infection have been identified by the *Transfusion Medicine Epidemiology Review* (TMER), a collaborative project between the *UK NCJDRSU* and *UK Blood Services* (UKBS) [18]. The identification of three vCJD cases in the small cohort of recognized recipients of blood transfusions from subjects incubating vCJD, linked to the fact that two of these cases were associated with a common blood donor, showed unequivocally that blood transfusion was a transmission route for vCJD. To date, just remain alarmist uncertainties about the future number of vCJD cases, also possibly linked to secondary transmission (*i.e.*, man to man) from sub clinically infected people by way of medical treatments involving the use of vCJD-contaminated blood products [19,20].

Indeed, like asymptomatic carriers of other well known blood-borne infections, e.g. hepatitis and human immunodeficiency virus (HIV), subclinical carriers of the vCJD infectious agent may transmit infection by medical instruments, blood and organ donation [21,22]. However, the big difference between vCJD and the other blood-born transmissible diseases is that for vCJD, unfortunately to date, no validated diagnostic test is available yet [23].

CONCLUSIONS

The history of BSE/vCJD epidemic risk clearly demonstrated that complex issues rarely have simplistic solutions. We learned important lessons from BSE/vCJD crisis: the need for an integrated, *holistic* approach to *risk assessment* (so-called "*One Health approach*", <*http://www.cdc.gov/onehealth/about.html*>), for identifying critical common control points and comparing the costs and the efficacy of the adopted intervention strategies; the pivotal importance to provide a correct risk communication, and importantly, the need for implementation of legislation and regulatory authorities for dealing with emerging (and re-emerging) infectious diseases.

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