Atypical variants of bovine spongiform encephalopathy: rare diseases with consequences for BSE surveillance and control

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Abstract

Occurring for the first time in 1986 in the United Kingdom, bovine spongiform encephalopathy (BSE), the so-called "mad-cow disease", has had unprecedented consequences in veterinary public health. The implementation of drastic measures, including the ban of meat-and-bone-meal from livestock feed and the removal of specified risk materials from the food chain has eventually resulted in a significant decline of the epidemic. The disease was long thought to be caused by a single agent, but since the introduction of immunochemical diagnostic techniques, evidence of a phenotypic variation of BSE has emerged. Reviewing the literature available on the subject, this paper briefly summarizes the current knowledge about these atypical forms of BSE and discusses the consequences of their occurrence for disease control measures.

Keywords: bovine spongiform encephalopathy (BSE), atypical bovine spongiform encephalopathy (atypical BSE), Switzerland, surveillance, control measures

Atypische Varianten boviner spongiformer Enzephalopathie: seltene Krankheiten mit Konsequenzen für die BSE-Überwachung und -Bekämpfung

Mit dem ersten Auftreten im Jahr 1996 im Vereinigten Königreich hatte die Bovine Spongiforme Enzephalopathie (BSE), der sogenannte Rinderwahnsinn, beispiellose Konsequenzen für das öffentliche Veterinärwesen. Die Umsetzung drastischer Bekämpfungsmassnahmen, wie das Verfütterungsverbot von Fleisch-Knochen-Mehlen an Nutztiere und die Entfernung von spezifizierten Risikomaterialien aus der Lebensmittelkette haben schliesslich zu einem signifikanten Rückgang der Epidemie geführt. Für lange Zeit ging man davon aus, das die Krankheit von nur einem Typ des Erregers verursacht wird. Seit der Einführung von immunochemischen diagnostischen Verfahren zeigten sich aber Hinweise auf phenotypische Varianten von BSE. Dieser Übersichtartikel fasst die verfügbare Literatur und den aktuellen Wissensstand zu diesen atypischen BSE Varianten zusammen und diskutiert mögliche Konsequenzen ihres Auftretens für die Seuchenbekämpfung.

Schlüsselwörter: Bovine Spongiforme Enzephalopathie (BSE), atypische Bovine Spongiforme Enzephalopathie (atypische BSE), Schweiz, Seuchenüberwachung, Seuchenbekämpfung

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Introduction

Bovine spongiform encephalopathy (BSE) is an acquired transmissible spongiform encephalopathy (TSE) in cattle and was described for the first time in two cows by late 1986 in the United Kingdom (Wells et al., 1987). Since then, more than 180'000 cases have been diagnosed worldwide with 468 cases in Switzerland (Fig. 1). Feeding of meat-and-bone-meal (MBM) has been identified as the main risk factor for BSE and is the vehicle for BSE transmission in cattle (Wilesmith et al., 1988). Thus, the most important measure of disease control is the ban of mammalian MBM in feed intended for farmed livestock. This measure proved to be very effective and many countries, including Switzerland, are now classified as having a negligible BSE risk by the International Animal Health Organization (OIE).

TSEs are characterised by a slow degeneration of the brain tissue, resulting in neurological disease and inevitably in death. They are caused by the accumulation of misfolded isoforms (PrP^d) of the normal physiological cellular prion protein (PrP^c) (Prusiner et al., 1998). The BSE epidemic was caused by oral PrP^d uptake via contaminated MBM (acquired TSE). In human TSEs, such as Creutzfeldt-Jakob-Disease (CJD), PrP^d can be generated spontaneously (sporadic CJD) or occur secondary to mutations of the prion protein encoding gene (genetic CJD) (Prusiner, 1996). The key event in the disease pathogenesis is that PrP^d serves as a seed for conversion of PrP^c into PrP^d, which eventually results in PrP^d aggregation and neurotoxicity.

There is irrefutable evidence of the existence of prion strains (Bruce and Fraser, 1991). These can be discriminated on the basis of their biological properties, i. e., the host spectrum, incubation period, neuropathological lesions, clinical symptoms as well as biochemical characteristics of PrP^d, such as resistance to proteolytic degradation, the migration pattern in Western immunoblot and the reactivity against different antibodies. Nevertheless, it is also possible for prions to switch strain characteristics, especially on the occasion of inter-species transmission (Beringue et al., 2007; Capobianco et al., 2007; Seuberlich and Zurbriggen, 2010; Baron et al., 2011).

For many years, it was believed that BSE in cattle was a uniform disease caused by a single prion strain. However, in 2004 evidence of variations of strain characteristics of BSE were reported by two research groups from France and Italy independently (Casalone et al., 2004; Biacabe et al., 2004). Transmission studies to rodent models and cattle confirmed that these so called atypical BSE cases were caused by prion strains distinct from that of the classical BSE type (C-BSE) (Baron et al., 2006; Buschmann et al., 2006; Lombardi et al., 2008; Okada et al., 2011). Similar atypical BSE cases have later been identified in many countries, including Switzerland. Here we aim at summarizing the current knowledge about atypical forms of BSE and discuss the consequences of their occurrence for disease control measures.

Characteristics of atypical BSE cases

So far, two types of atypical BSE have been described: H-BSE and L-BSE. The prefixes H and L refer to a higher and lower molecular mass of PrP^d in Western blot analysis compared to C-BSE, after partial proteolysis by proteinase K (Fig. 2) (Jacobs et al., 2007). Other discriminatory criteria are the relative proportion of PrP^d glycoforms (for L-BSE) and reactivity against N-terminal PrP specific antibodies (for H-BSE). Western blot techniques are now established in national and OIE reference laboratories to determine the BSE type. Worldwide around 100 cases of H- and L- BSE have been identified since 2004. Many of them were found retrospectively in animals that had previously been diagnosed as BSE cases, but without further classification. The vast majority of atypical BSE cases was found by active surveillance programs in fallen stock, regular slaughtered and emergency slaughtered animals. Thus, little is known about the clinical signs in L- and H-BSE. Data from experimental transmission studies in cattle suggest that
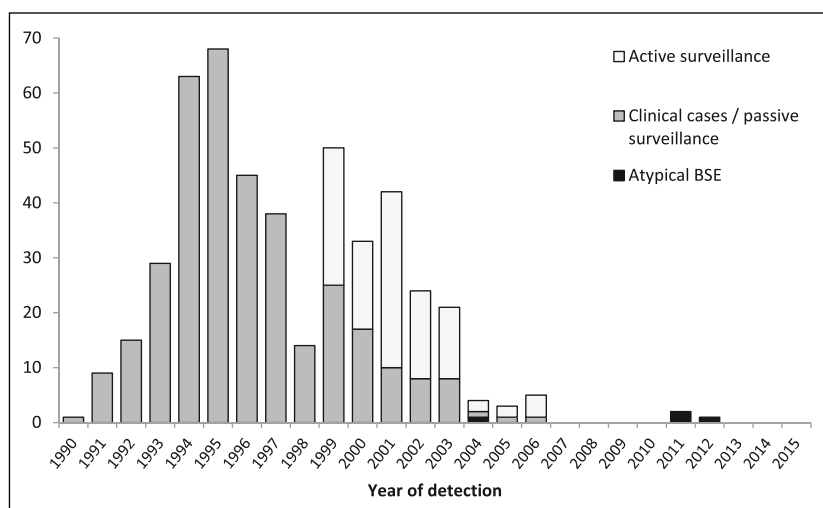
Figure 1: Cases of bovine spongiform encephalopathy (BSE) in Switzerland, per year. Case numbers dropped approximately five years after the ban of meat-and-bone meal from ruminant feed (first feed ban) came into force in 1990, which corresponds to the mean incubation period of BSE. Because BSE cases occurred also in animals that were born after 1990, the feed ban was reinforced in 2001 by excluding MBM from feed intended for poultry and pigs as well. Until 1998 surveillance was purely passive. The introduction of active surveillance in 1999 led to a 3-fold increase of case numbers. The last case of C-BSE was diagnosed in 2006. Atypical BSE cases are indicated in black and comprise two H-BSE cases (2004, 2012) and two aberrant cases (2011) that are currently under detailed investigation.
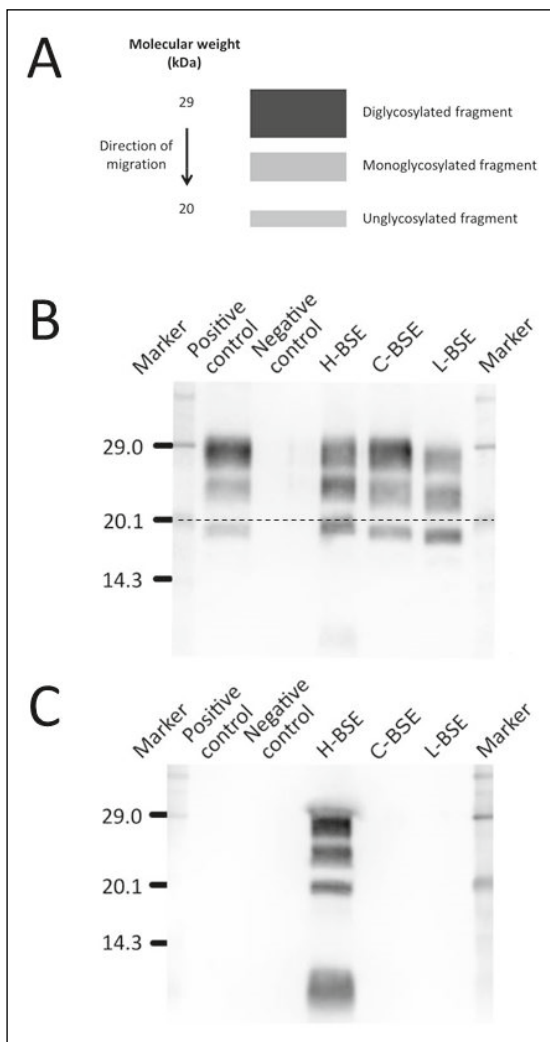
Figure 2: Differentiation of Bovine spongiform encephalopathy (BSE) types in Western Blot. **A,** Schematic migration pattern of PrP^d after proteinase K treatment (PrP^{res}). **B,** Western immunoblot using the core antibody Sha31. PrP^{res} of all three BSE types are labelled, but has slightly increased (H-BSE) or decreased (L-BSE) molecular mass compared to C-BSE. This feature reflects differential N-terminal processing of the prion protein by proteinase K. In L-BSE, the proportion of diglycosylated PrPres moiety is smaller than in other types. **C,** The N-terminal antibody 12B2 binds only to PrPres of H-BSE.

cases of C-BSE, such as Sweden and Norway. Thirdly, their case numbers remained stable over the years, while those of C-BSE constantly declined (Biacabe et al., 2008). Finally, in several countries atypical BSE has been detected in cattle that were born after the implementation of the feed-ban. All this argues for atypical BSE being unrelated to the C-BSE epidemic and to the feeding of MBM. While a mutation of the prion protein encoding gene supported a genetic etiology in one of the H-BSE cases reported from the USA, this could not be confirmed in any L- or other H-BSE cases (Richt and Hall, 2008). Taken together, this supports a widely accepted hypothesis that H- and L-BSE are sporadically occurring prion diseases similar to the sporadic type of CJD in humans.

Atypical BSE in Switzerland

In Switzerland two cases of H-BSE have been detected (Fig. 1). The first was diagnosed in 2004 in a 19-year old miniature zebu held in a zoological garden. This animal showed neurological clinical signs and was reported as BSE suspicion to the authorities (Seuberlich et al., 2006). The second case was diagnosed in 2012 in a 6.5 years old cow after emergency slaughter and BSE testing in the framework of the Swiss statutory active surveillance program (Guldimann et al., 2012). This animal was imported from Germany at the age of 17 months, i. e. in 2005. In addition, two cattle with a positive PrP^d signal in brain samples have been identified in Switzerland in 2011. The PrP^d Western blot profile in these animals did not match those of C-, L- or H-BSE but represented a truncated prion protein fragment (Seuberlich et al., 2012). The significance of the findings in the 2011 cases remains unresolved for the moment. Bioassays in cattle and mice are under way to determine whether they are related to prion infectivity. Retrospective studies on cases previously classified as C-BSE did not uncover additional cases of atypical BSE in Switzerland, indicating that these diseases are rare events (Siso et al., 2007; Tester et al., 2009).

Atypical BSE and disease control

If H- and L-BSE are truly sporadic, affected animals are expected to be present at a low but constant level in the cattle population, independently of control measures established for C-BSE. This implicates that their eradication may never be achieved.

A point that needs to be remembered is that the origin of the C-BSE epidemic still remains enigmatic. For many years, the main hypothesis was that it arose from the inter-species transmission of a British scrapie prion

clinical signs include abnormal gait and posture, anxiety, dullness, recumbency, as well as loss of proprioceptive control (Lombardi et al., 2008; Okada et al., 2011; Konold et al., 2012). In this regard, they appear to be similar to the wide and unspecific spectrum of signs observed in C-BSE, but importantly also in other neurological diseases in cattle (Braun et al., 1997). Despite these similarities there are some important particularities in atypical BSE cases. First, animals with atypical BSE were found to be older (mean age ~12 years) compared to those diagnosed with C-BSE at the peak of the epidemic (mean age ~5 years). Secondly, atypical BSE has been reported from countries that did not diagnose

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strain that had been insufficiently inactivated during the MBM production (Wilesmith et al., 1988). However, experimental transmission of scrapie to cattle was only possible by intracerebral inoculation, but not by oral exposure, and resulted in a disease phenotype that was clearly distinct from C-, H- and L-BSE (Konold et al., 2006; Konold et al., 2013). These findings raised doubts about the scrapie hypothesis. By contrast, both L- and H-BSE readily transmit to cattle by intracerebral inoculation, and the H- and L-BSE specific phenotypes are essentially maintained after primary passage (Konold et al., 2014). Strikingly, both variants have shown a potential to convert to a prion strain indistinguishable from C-BSE upon serial passage in some rodent models (Beringue et al., 2007; Capobianco et al., 2007). Therefore, an alternative scenario for the origin of C-BSE is that atypical BSE prions have entered the feed-chain, and converted their strain characteristics upon serial passage in cattle or other intermediate hosts. In this sense, atypical BSE may have been at the origin of the BSE epidemic. Yet, a major gap in our knowledge is whether atypical BSE strains are transmissible by the oral route and by the feeding of MBM. Because MBM is a high protein and energy supplement for animal feed, the question of reintroducing this feeding to livestock is a sensitive issue. The possibility of atypical BSE being the origin of the C-BSE epidemic is a strong argument against the readmission of MBM in cattle feed, even at times when C-BSE is eradicated.

Atypical BSE and public health

A major concern is BSE transmission to humans. Scientists from the UK established a link between C-BSE in cattle and a newly emerging variant of CJD (vCJD) in humans in the mid-1990s (Will et al., 1996). Cattle-to-human transmission is supposed to have occurred through ingestion of infected bovine tissue (Hill et al., 1997). More than 220 people died of vCJD in the past 20 years. The most important measure to minimize exposure of humans to the BSE agent is the removal of specified risk material (SRM) of cattle from the food-chain. While the link between C-BSE and vCJD is supported by epidemiological evidence, i. e. by spatial and temporal association, there is no such evidence for H- and L-BSE being related to a human TSE. Yet, this picture may be biased by the low prevalence of both atypical BSE as well as human TSEs.

The definition of SRM is based on scientific evidence and risk assessments, and includes bovine tissues that have demonstrated to contain a significant amount of C-BSE infectivity in bioassays. Similar investigations for H- and L-BSE have not been conducted, but different methods have shown the presence of both the H- and

the L-BSE PrP[d] in the CNS, retina and some peripheral nerves (Hagiwara et al., 2007, Iwamaru et al., 2010, Okada et al., 2011). There is no evidence for significant amounts of PrP[d] or infectivity in tissues other than those currently defined as SRMs, but systematic investigations on the pathogenesis and tissue distribution of atypical BSE prions in cattle are still missing. A detailed protocol to study these aspects has recently been proposed by the European Food Safety Agency, but such studies are complex and will take several years to be completed (EFSA, 2014).

The question of a zoonotic potential for atypical BSE has been addressed in a series of studies. L-BSE but not H-BSE transmitted to mice transgenic for the human prion protein (Beringue et al., 2008; Kong et al., 2008), thus L-BSE prions may induce a TSE on a human prion protein background. However, these results could not be confirmed in a different human transgenic mouse line (Wilson et al., 2012). Of greater concern is the successful transmission of L-BSE to primates by intracerebral injection (Comoy et al., 2008; Ono et al., 2011; Mestre-Frances et al., 2012), but also after oral challenge (Mestre-Frances et al., 2012). Transmission of L-BSE was even more efficient than that of C-BSE under similar conditions, however experiments on H-BSE transmission to primates have not yet been completed. Taken together, this indicates that L-BSE prions may infect humans. Whether this also counts for H-BSE prions remains unclear. In conclusion, it will be important that any changes in the current SRM list also consider the risk for public health related to atypical BSE transmission.

Disease surveillance

A prerequisite to monitor the efficiency of disease control is continuous disease surveillance. The International Animal Health Organization (OIE) has established minimal requirements for BSE surveillance programs (OIE, 2014). Surveillance systems should allow the detection of BSE around a prevalence of at least one case per 50'000 adult cattle with a confidence level of 95% in order to maintain the status of negligible BSE risk. To fulfil these requirements, most countries combine active with passive surveillance. Active surveillance consists in large scale testing of perished and slaughtered animals, while passive surveillance is based on the recognition, reporting and laboratory investigation of cattle with neurological signs indicative of BSE. Atypical BSE cases have mostly been identified by active surveillance and in countries that relied on testing of large numbers of slaughtered cattle and fallen stock. The prevalence of H- and L-BSE has been estimated as low as ~1 case per 3 million adult cattle (Buschmann et al.,

2006; Biacabe et al., 2008). Therefore, the detection of atypical BSE cases may become a rare event in countries with mainly active surveillance systems that do not considerably exceed the OIE requirements. The OIE system has been primarily designed to assess the efficiency of control measures for C-BSE. It is likely that the MBM ban in feed for non-ruminant species will be relaxed in the near future in some countries (Anonymus, 2010). In this scenario it will be important to maintain a high level of surveillance, in order to detect any reintroduction, re-emergence and re-circulation of prion diseases in the cattle population. Active BSE surveillance is costly and many countries have reduced the amount of testing over the past years. This situation emphasizes the importance of passive surveillance, which was very effective in the identification of BSE cases in the early years of the epidemic in Switzerland. However, at that time the disease was massively present in the media and disease awareness was high. In more recent years the disease awareness dropped and reporting of cattle with neurological disease became uncommon, with less than 10 suspect cases being notified each year (Fig. 3). These numbers need to be increased in order to provide sufficiently sensitive disease surveillance and to maintain the negligible BSE risk status of Switzerland in the future.

Conclusion

Twenty-five years after the identification of the first case of BSE in Switzerland, the epidemic has been successfully controlled. The finding of atypical cases of BSE at a very low prevalence challenges future disease control strategies. Yet, the knowledge on the transmissibility and zoonotic potential of atypical variants of BSE is still limited and further research in this direction is needed. If occurring truly sporadically, atypical BSE will never be eradicated and may represent a constant risk for the re-introduction and re-circulation of prion diseases into the cattle population, and for public health. Any changes in the disease control measures need to take this situation into account and must involve continuous and efficient disease surveillance. However, active surveillance programs are costly and the reporting rates of BSE
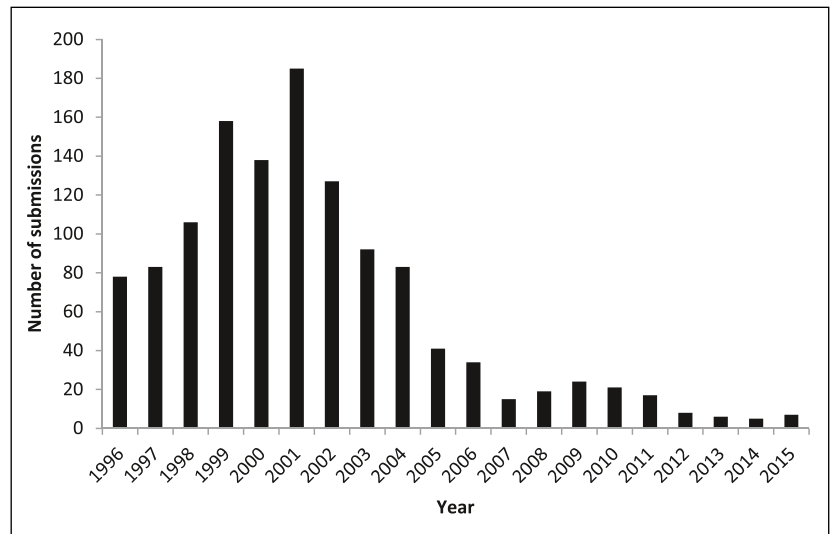

Figure 3: Submissions of cattle samples to neuropathology diagnostic services at the NeuroCenter, University of Berne (1996–2015). Numbers are shown regardless of the final diagnosis and decreased considerably after the last cases of classical BSE in 2006.

suspect cases in the framework of passive surveillance have dramatically declined. This situation is additionally hampered by the fact that classical and atypical BSE cases often do not present specific clinical signs allowing for a clear differentiation from other neurological diseases. A unified approach would be the expansion of passive surveillance to neurological cattle diseases in general and to increase the proportion of such cases submitted to neuropathology diagnostic services. Targeted laboratory testing for specific pathogens in combination with a systematic histopathological brain examination could deliver real-time data on the prevalence of neuroinfectious diseases in cattle and contribute to early-warning and disease surveillance strategies for emerging and re-emerging diseases also beyond BSE.

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Variantes atypiques de l'encéphalopathie spongiforme bovine: maladies rares avec des conséquences pour la surveillance et la lutte contre l'ESB

L'encéphalopathie spongiforme bovine (ESB) dite aussi „maladie de la vache folle", apparue pour la première fois en 1996 au Royaume-Uni, a eu des conséquences sans équivalent pour le service public vétérinaire. La mise en application de mesures de lutte drastique, telle l'interdiction d'affourager les animaux de rente avec des farines animales et le retrait de la chaine des aliments de matériels à risque a conduit à un recul significatif de l'épidémie. Durant longtemps on a considéré que la maladie n'était causée que par un seul type de l'agent infectieux. Avec l'introduction de techniques de diagnostic immunochimiques, on a toutefois des indices de variantes phénotypiques de l'ESB. Le présent article résume la littérature disponible et fait le point des connaissances quant à ces variantes atypiques de l'ESB; on y discute également les conséquences possibles de leur apparition quant à la lutte contre la maladie.

Varianti atipiche di encefalopatia spongiforme bovina: malattie rare, che comportano implicazioni per la sorveglianza e il controllo della BSE

Con la sua prima apparizione nel 1996 nel Regno Unito, l'encefalopatia spongiforme bovina (BSE), il cosiddetto morbo della mucca pazza ha avuto conseguenze senza precedenti sul sistema veterinario pubblico. L'attuazione di drastici mezzi di controllo, come ad esempio il divieto di somministrazione di pasti a base di carne-ossa per gli animali da allevamento e la rimozione di materiali specifici a rischio dalla catena alimentare hanno infine portato ad un calo significativo dell'epidemia. Per tanto tempo si è pensato che la malattia fosse causata da un solo tipo di agente patogeno. Dall'introduzione di metodi diagnostici immunochimici si sono scoperte evidenze di varianti fenotipiche della BSE. Questo articolo riassume la letteratura disponibile e lo stato attuale delle conoscenze su queste varianti atipiche di BSE e commenta le possibili conseguenze della loro comparsa per il controllo delle malattie.

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