

CLINICAL SIGNS OF BOVINE SPONGIFORM ENCEPHALOPATHY IN CATTLE

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Introduction

The agent causing BSE in cattle is believed to be a uniform strain based on neuropathological findings in brains of cattle with BSE [1-3] and transmission studies in mice [4,5]. However, a new type of encephalopathy has first been described in Italy, which differed from BSE in its neuropathological and biochemical properties and was termed BASE (Bovine Amyloidotic Spongiform Encephalopathy) [6]. Similar cases have since been detected in other countries and these “unusual” BSE cases have been re-classified as either H-type BSE or L-type BSE (including BASE) depending on the Western blot profile of digested brain material, which showed a protein band of the unglycosylated form of disease-associated PrP of either higher (H-type) or lower (L-type) molecular mass than samples from “classical” BSE [7]. All cases have so far been detected in mainly aged cattle (8-15 years) by surveys of either apparently healthy slaughtered cattle or fallen stock, and it has to be assumed that the clinical signs – if any – are very unspecific and unlike those of the vast majority of BSE cases found in Europe. The following sections describe the clinical signs usually associated with BSE (now called C-type). Other prion diseases in cattle are described further below.

Case History

Age, sex, breed and genotype

Most BSE cases have been diagnosed in 4 to 6 years-old cows (range 20 months-18 years). Cases have been more frequent in dairy cattle, but this may reflect the differences in feeding practices and life span. The main risk factor for BSE is still believed to be the feeding of contaminated feedstuffs. There does not appear to be any clear sex, breed or genotype predisposition that could be used as a clinical criterion despite recent studies that reported a higher incidence in cattle of certain genotypes [8,9] or breeds [10]. A

genetic basis for the occurrence of cases born after the reinforced meat and bone meal ban in the UK was not found [11].

Herd and Farm Parameters

Clinical BSE is rare. In most cases, only a small proportion of the animals is affected at or near the same time.

Rate of onset, progression & sequence of clinical signs

The exact onset of BSE may be difficult to determine because of the unspecific nature of the prodromal and early clinical signs. BSE typically begins insidiously and the progression from prodromal signs to overt clinical disease may take weeks to months. Apparent clinical remissions have been reported in early cases, which later progressed.

The mild behavioural changes of early BSE cases are more likely to be detected when animals are known and handled individually on a regular basis, such as for daily milking in dairy cattle. Separation from the herd, dullness, and bullying are also best seen during observation of the animals at rest and in their usual environment. Early signs of BSE are unlikely to be detected in cattle that are observed infrequently or without being handled. In such circumstances, more BSE cases may be presented acutely rather than with the typical BSE history of a slowly progressive illness.

Another factor that impacts on the detection of BSE is the degree of awareness of the clinical signs of BSE. In spite of the large overall number of cases seen over the years, BSE remains a sporadic and rare disease that is encountered only rarely (if at all) by individual farmers and veterinarians. Without a good awareness of BSE, it may not be considered in the list of possible disease causes and BSE cases may be presented for culling because of adverse but non BSE-specific changes and before they display the full array of clinical signs. Such adverse changes might be an unmanageable behaviour (e.g. kicking in the milking parlour), weight loss, a decrease in milk production, or recumbency (the latter likely to have resulted from an injury in a fall caused by an undetected neurological deficit). The risk of missing an early BSE case is reduced if animals with early non-specific signs are examined in detail and challenged to ascertain whether more definite clinical signs might be induced. Challenges that may enhance the expression of the clinical signs of BSE are any procedures that are not familiar to the animal, such as

restraint or confinement in handling stocks for examinations, blood sampling or movement to unfamiliar territory. In some cases, this can be even achieved by exposing the animal to an unexpected object (e.g. a bucket or a shovel) in its familiar environment ([see video](#)). Forced exercise and circulation across new grounds may also enhance apprehension and the expression of minor gait deficits.

The stresses of transportation, parturition or concurrent illnesses may precipitate the onset and/or the progression of BSE.

If left to run its course, BSE irremediably progresses to severe signs that warrant slaughtering, in particular severe gait deficits. Early in the epidemic, it was shown that at least one of the three most typical signs of BSE (apprehension, hyperaesthesia or ataxia) was identified in 97% of 17,154 cases [12].

Changes in mental status & behaviour, hyperaesthesia & movement disorders

Hypervigilance, apprehension, aggressiveness & status within herd

Hypervigilance and restlessness when approached are major signs of BSE. This is mostly observed in response to husbandry routines. This state of hypervigilance is usually described as apprehension or increased fearfulness [13]. BSE cases are often the first to rise upon approach and they either 'freeze' or move away from the herd to the farthest area while intensely staring at visitors and interrupting their activities for a longer time than their herd-mates. In contrast, normal herd mates will usually take little or no notice of visitors, or come forward to a familiar visitor. Instead of staring, some BSE cases may turn around and stay in the farthest part of the pen facing a corner or wall, apparently to evade sight. The intense staring of BSE cases has been described as 'the BSE look' (see Fig. 1) and may make ocular structures appear 'different' or more prominent. While staring at visitors or attendants, BSE cases typically appear disturbed and anxious and may raise or lower their heads alternately. This may be associated with threatening movements such as head butting, charging, pawing or stamping at the ground and/ or snorting. These behaviours are often referred to as 'defensive aggression' because they usually only occur upon approach and when animals are confined and cannot flee away from visitors. Less

frequently but very dangerously, BSE cases may show unprovoked aggression towards people ([see video](#)).



Fig. 1
'Staring expression'

BSE cases may keep away from their herd-mates and come last to feed or to the milking parlour, possibly because they have become fearful of their herd-mates or environment. Less frequently, BSE cases may also display unprovoked aggression towards other cattle.

Dullness may be observed when animals are monitored undisturbed over prolonged periods. After some time, BSE cases may settle down and appear dull and inactive in comparison with herd-mates, they may also spend time facing walls.

Restraint difficulties & panic reactions

The unpredictable kicking and other exaggerated reactions of BSE cases make them difficult and often dangerous to handle. Great caution must be taken to approach BSE cases and their restraint should not be attempted outside sturdy and safe restraining devices. Unfamiliar surroundings or handling, in particular when accompanied by sudden movements, may provoke 'panic' reactions. Animals may also stop, startle, tremble or become nervous when coming to cross a previously familiar line on the ground (doorway, pen threshold, bright light reflection on the ground, drain cover or gutter). They may refuse to proceed over these lines as if there was a major physical obstruction. If they can be forced forward, they may take a giant leap over the perceived obstacle. This problem can usually be overcome by spreading bedding over the offending to mask it ([see video](#)).

BSE cases usually try to evade any approach or physical restraint. When restrained, they may vigorously 'head butt', especially when approached or touched on the head and neck ([see video](#)).

Hyperaesthesia, 'BSE series' & ballistic kicking

The hyper-reactivity of BSE cases to certain environmental clues or external stimuli is often described under the term 'hyperaesthesia'. This may be due to one or more nervous system lesions resulting in hyperaesthesia, hyperreflexia or a desinhibition of lower motor systems. Suspect cases may suddenly back away from any gentle hand approach ([see video](#)). The exaggerated events often seen in BSE cases are listed in Table 1. These prolonged and magnified responses may be quantified during routine testing of the function of the cranial nerves.

Table 1. 'BSE EVENTS or BSE SERIES OF EVENTS'

BSE cases may show an increased frequency of one or more of the events listed in this table, either spontaneously or triggered by stress or external stimuli.

'BSE EVENTS' (may occur spontaneously or be provoked by an stimulus that was previously insignificant to the animal)

- *Excessive and asymmetrical ear movements*
- *Head and neck shaking, head tossing, head bobbing*
- *Sneezing, snorting*
- *Excessive nose licking, nose wrinkling, yawning or flehmen*
- *Tooth grinding (bruxism)*
- Tremors
- *Agitated behaviour*
- *Excessive vocalisation*
- *Unusual hiding, going away in familiar circumstances, including going to face a wall or a corner*
- *Over-reaction to visual or auditory stimuli that are part of the normal routine and insignificant to other cattle*
- *Sudden jerking movements of limbs, body parts or whole body (startle)*

EVENTS MOSTLY SEEN WHEN AN EXTERNAL STIMULUS IS APPLIED

- Startle (sudden jerk of the head, forequarters or whole body)
- *'Pawing at the ground' and blowing air forcefully while facing an observer*
- *Violent kicking*
- *Aberrant startle (drop attacks?): advanced BSE cases may fall over as they startle*

'BSE SERIES of EVENTS'

Any series of the events occurring in a close temporal combination is most suggestive of BSE, especially if it can be induced in a repeatable fashion by an external stimulus.

Tests of Hyper-reactivity

Tactile Stimuli and Stick Test

Exaggerated responses to tactile stimuli (e.g. head tossing) are usually severe when the head or neck is touched and decrease caudally ([see video](#)). These responses are often elicited by purely standing in front of an animal that is restrained in a crush. Stroking of the tail head may have a calming effect.

Some BSE cases show quick and forceful 'ballistic' kicking of the hind limbs, which is sometimes repetitive and often leads to early drying off. Touching the hind limbs of BSE suspects should be avoided, unless using a long & flexible stick. This ballistic kicking may occur spontaneously, especially when cattle are being approached from the side or from behind. This reaction may be tested with a flexible plastic ('PVC') stick to apply a light touch on the lower hind limbs ('stick test'). In BSE, this may induce 'ballistic' kicking of the stimulated limb ([see video](#)). By contrast, normal cattle may show no reaction to this test or they may kick on the first stimulus (usually not forcefully) and stop kicking after the second or third stimulus. Given the potential for serious backlash injuries to the animal or handlers during kicking, we strongly advise against using an inflexible hard stick device (broomstick or other) for this test.

Flash Test, Bang Test or Hand Clap and Clipboard Test

Startle reactions are common in BSE cases and may be defined as an exaggerated motor response to unexpected visual, tactile or auditory stimuli. This may take the form of a flinch or jerk of the head, forequarters or of the whole body. Episodically, BSE cases may

show sudden jerking of a limbs, head or whole body startle in the absence of any apparent stimulus (unprovoked startle response) ([see video](#)). Most typically, many BSE cases will repeatedly startle in responses to visual, tactile or auditory stimuli [14,15]. Startle responses may be evoked by sudden loud noises ('hand clap' or 'bang test' ([see video](#)), sudden lighting changes ('flash test' ([see video](#))), tactile stimuli or abrupt movements such as a brisk hand approach towards the face ([see video](#)) or a waving of a clipboard ([see video](#)) [15]. They typically show no habituation to a repeated stimulus. This is in contrast with most normal cattle, which usually will quickly become accustomed to most stimuli after an initial mild flinching or startle response (surprise response). Adventitious movements (muscle fasciculations, tremors or myoclonus) or head bobbing and tossing may follow startling events (see 'BSE series', Table 1). In extreme cases, startle reactions may culminate in falling, collapsing or seizure episodes.

Other adventitious movements (muscle fasciculations, head bobbing, tremors, myoclonus) and seizures

There may be an increased frequency or excessive duration of superficial muscle fasciculations (of the shoulders, flanks and limbs), tail movements or head and neck shaking or tossing towards the flank. These events may occur in the absence of any obvious exogenous stimuli or be evoked by stress, movements or by insignificant stimuli such as flies, falling feed debris or nearby movement of a person or herd-mate (see 'BSE series', Table 1).

As the disease progress, there may be tremors involving the head and neck, the whole body and/ or the limbs ([see video](#)). Excessive head shaking may take a pathological and stereotypic form resembling the head bobbing seen in some cerebellar lesions. As for muscle fasciculations, tremors and head bobbing may occur spontaneously or they may be triggered or worsened by stress (see 'BSE series', Table 1) and by locomotion. Myoclonus and seizures have also been reported, but apparently only in very advanced BSE cases.

Miscellaneous head signs

The following signs have often been attributed to unspecified disturbances of sensory or autonomic cranial pathways.

Excessive nose licking, nose wrinkling, snorting, yawning

BSE cases often display excessive or prolonged episodes of nose licking, nose wrinkling, sneezing, snorting, coughing or yawning, which may occur in single episodes or in repetitive combinations and sometimes together with the other events listed in table 1. Flehmen may also follow such episodes (see [video](#) and also [video](#)).

Signs that suggest pruritus: head rubbing

Pruritus, alopecia and self-inflicted skin lesions are not as frequent as in scrapie ([see video](#)). Head rubbing may be very vigorous and may cause alopecia or benign skin lesions on the poll region of the head. A positive scratch response is displayed rarely [16].

Teeth grinding (bruxism)

Teeth grinding has been frequently associated with BSE (reported in approximately 40% of cases [12,17]). It may occur during BSE series or independently of any triggering stimulus ([see video](#)).

Ptyalism

In our experience, spontaneous ptyalism is infrequent in BSE. However, stressed and aggressive BSE cases will very frequently display severe ptyalism upon approach, handling or stimulation.

Posture and locomotion changes

Postural and locomotion disturbances are often mild or absent in early BSE cases. At first, affected cattle may appear 'stiff' and refuse to walk or run. Subtle gait deficits may be best evidenced when the animal is made to walk, turn, go over steps or slopes and then run at slow and faster paces.

The more advanced BSE cases may show a wide based stance and a low head carriage ([see video](#)). They may have difficulty getting up, at times showing a period of 'dog sitting' in the process [18] (see Fig. 2). In some cases, there is a lumbar kyphosis with dropping of the hindquarters and the hind limbs are placed forward, underneath the abdomen.



Fig. 2 Dog sitting posture

Weakness, paresis and incoordination of the gait (ataxia) are usually first noticed in the hindquarters. There may be lateral swaying and (or) dropping down of the hindquarters and an increased frequency of stumbling, slipping or falling. Pacing has also been observed [19]. Knuckling of the fetlocks is an infrequent feature of BSE, which was reported in less than 10% of cases early in the epidemic [12,16]. Spasticity, postural tremors and ataxia become more severe as the disease progresses. A mild degree of hypermetria may be present in addition to spasticity ([see video](#)). Progressive neurogenic gait deficits may eventually lead to recumbency. One or both hind limbs may be stretched out behind in recumbent cattle [20] (Fig. 3).

Recumbent cattle should be considered as BSE suspects unless an alternate cause of recumbency can be clearly established.



**Fig. 3
Cow in sternal recumbency with
both hind limbs stretched out
behind**

Other historical and physical examination findings

BSE cases typically have normal temperature and mucous membranes. Their respiration rate may be increased when examined in an agitated state. One or more of the following signs may also be noted.

Weight loss and loss of condition

Loss of weight and condition (see Fig. 4) is a frequent feature of BSE and may be its very first sign.



Fig. 4. Loss of bodily condition

(note the prominent hip bone and the clearly visible rib cage)

Traumatic lesions and / or recumbency

Violent kicking may also result in lesions on the hind limbs.

BSE cases also frequently show traumatic lesions of the skin and deeper tissues, such as lacerations, contusions, haematomata, seroma or other swellings. This may be caused by accidents (slipping, falling or bumping into race sides and fences), which may or may not be witnessed and may result from subtle and otherwise undetected weakness or neurological deficits. Such accidents may also lead to recumbency and inability to stand, often described under the umbrella of 'downer cow' syndrome.

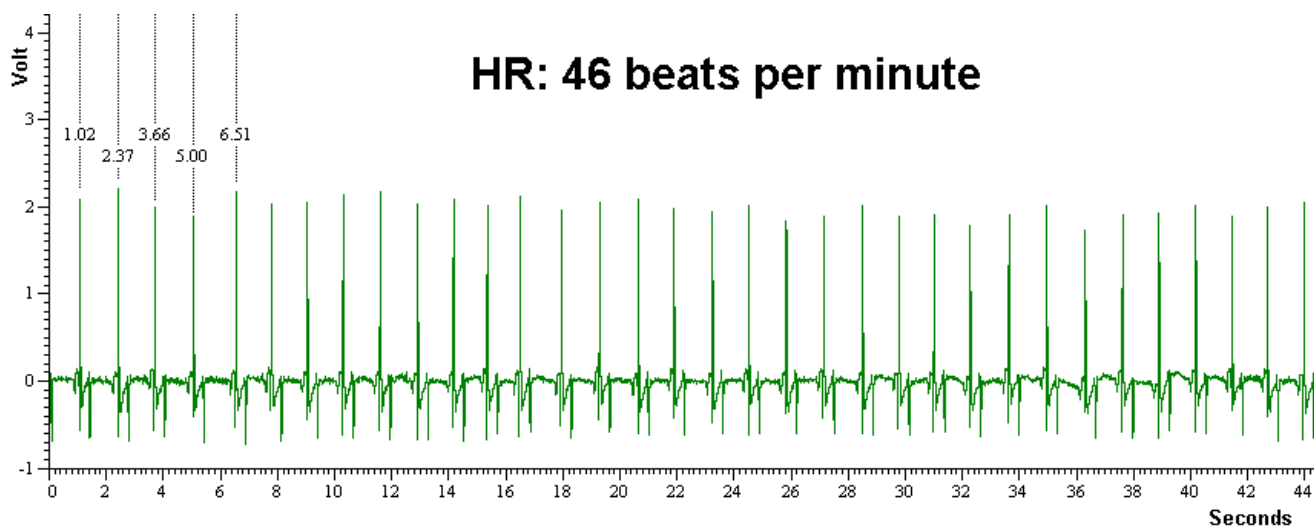
BSE should always be considered in the differential diagnosis of unexplained traumatic lesions and recumbency in cattle. This is particularly applicable to abattoirs, where the history of such lesions is not available. With the onset of active surveillance for BSE, it has been shown retrospectively that many of the cases diagnosed in abattoir surveys had displayed signs of BSE that had been overlooked, with presence of swollen joints, falling or recumbency in about 50% of cases [21].

Heart rate and blood pressure changes

Bradycardia and disturbances of the heart rhythm are frequently associated with clinical signs of BSE [22] (see Fig. 5). The most typical finding is that of a 'paradoxical bradycardia', in which the heart rate remains low (at around 60-80 beats per minutes or lower) whilst tachycardia would be expected as a result of the animal's obvious state of stress, fear or excitement.

BSE cases may also have an elevated blood pressure [23].

Fig. 5 Bradycardia in a cow with BSE



Rumination changes

BSE cases appear to spend as much time eating as normal animals but they appear to spend less time ruminating [24,25]. Eructation, swallowing and rumen contractions appear intact in most cases. There have been anecdotal reports of gastro-intestinal 'bloat' in BSE cases, which may reflect the average incidence of bloat in cattle.

Milk production

BSE cases may show a decrease in milk yield.

Decreased sensitivity to xylazine

BSE cases may show no or very little reaction to the administration of xylazine in a dose that would induce marked sedation in normal cattle [23].

Ancillary tests

Blood, urine and cerebrospinal fluid analysis

No change has been identified in BSE cases on routine haematology, biochemistry or cytology of the blood, urine or cerebrospinal fluid (CSF) [26-28]. One study failed to identify disease-specific biochemical changes in the pre-clinical stage although it indicated that the energy metabolism of dairy cows incubating BSE was subtly changed [29]. Further studies revealed that blood levels of lactic acid and various amino acids were significantly altered in BSE, which was attributed to the exaggerated stress response observed in BSE cases [30]. More recently, changes in the level of selenium, molybdenum and manganese in blood but not in CSF have been reported in cattle with BSE [31].

Special tests on CSF have been the object of various studies. The 14-3-3 protein levels did not appear to distinguish between healthy cattle and cattle displaying early signs of BSE [32]. An increased concentration of S-100 protein was found in the CSF of some BSE cases but not in their serum [33,34]. Apolipoprotein E and two unidentified proteins were detected in CSF of BSE cases but were absent in healthy controls [35].

Blood tests on some of the above and on other components generally struggled to deliver satisfactorily despite earlier promising results [36]. Conservation of samples for blood-based tests may also alter test sensitivity or specificity [37]. It is probable that the decline in BSE prevalence internationally will prevent the introduction and final development of such tests, if only because test material for development and evaluation will be in limited supply.

Electrodiagnostics

Electrophysiological tests are time-consuming, require special equipment and can only be used on cooperative animals, which is of limited practical value but may be useful for scientific research. Abnormal electroencephalogram recordings were reported in a study on a few BSE cases [38]. Measurement of parasympathetic activity from electrocardiograms in cattle revealed changes that were attributed to BSE [39,40]. Test sensitivity, specificity and reproducibility have not been determined.

DIFFERENTIAL DIAGNOSIS

In the absence of a diagnostic test to confirm BSE in live animals, BSE suspects must be killed to proceed with post mortem diagnosis. In early BSE cases, clear neurological deficits may be absent. Clinical signs may be common to BSE and many other diseases. Diagnosis and/or treatment of other potential causes of illness may take place. Testing and blanket therapy may be indicated, depending on the severity of signs and prognosis for recovery (cost/benefit analysis). Syndromes that share clinical features with BSE may be of extraneural or neural origin. Extraneural diseases include painful conditions, ectoparasitism, slow wasting diseases, ocular diseases and ovarian cysts, which mainly result in weight loss or behavioural changes. A list of the main neurological diseases that may be confused with BSE is provided in Table 2 (see also [41-43]). One distinctive feature may be the slow onset and the diffuse, symmetrical nature of the neurological deficits in BSE.

Once a suspicion of BSE has arisen, the BSE suspect must be placed under restriction and monitored for a progression of the signs. Restriction is maintained until the animal either fully recovers (from another disease than BSE) or it is killed and tested for BSE.

Table 2. NEUROLOGICAL DISEASES THAT MAY BE CONFUSED WITH BSE

(Disorders in bold fit best with the expected age at presentation and clinical signs of BSE, while those followed by an asterisk* are more likely to be encountered in younger animals)

AETIOLOGICAL CATEGORY	DISEASES
Degenerative, developmental disorders, anomalies*	Storage diseases, abiotrophies, etc. Malformations of the central nervous system (including cerebellar aplasia / hypoplasia seen in BVD/MD) & adjacent bony structures*
Metabolic, endocrine disorders	Hypomagnesaemia (grass tetany) Hypocalcaemia Nervous ketosis Hepatic encephalopathy
Nutritional	Polioencephalomalacia (=cerebrocortical necrosis, Thiamine/vitamin B1 deficiency)* Copper deficiency
Neoplastic, Infectious, inflammatory	Brain or spinal cord tumours Viral: Malignant Catarrhal Fever (MCF), rabies, Aujeszky's disease, Tick encephalitis, Borna disease, etc. Bacterial: epidural abscesses (e.g. salmonella), listeriosis Fungal: aspergillosis, cryptococcosis (rare) Parasitic: cysts or migration (sarcocystis, coenuriasis) Other infectious myeloencephalitides (miscellaneous agents)
Idiopathic	Brainstem chromatolysis (with hippocampal sclerosis) Cerebral oedema

Toxic syndromes	Tetanus, Botulism Miscellaneous plant toxins, mycotoxicoses e.g. Ryegrass staggers Urea poisoning / Ammonia Toxicosis Organophosphate and other insecticide toxicity Mercury poisoning, lead poisoning Salt poisoning
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Traumatic injuries	Vertebral fractures
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* Diseases that are more likely to be recognised earlier in life than BSE

Clinical diagnostic criteria

Estimation of BSE prevalence and assessment of the BSE status in a country is largely influenced by the degree of surveillance for BSE. Cattle displaying neurological diseases or cattle with conditions that require emergency slaughter belong to the highest risk group for BSE and it is important that these cattle are examined for the presence of signs associated with BSE.

Cases reported as suspects

Various clinical procedures have been proposed to detect BSE in live cattle [14,15,44,45]. Whilst it is generally acknowledged that cattle that exhibit signs of behavioural, sensory as well as locomotor abnormalities are most likely to have BSE [15,46], the presence of changes in only one or two categories (e.g. an animal that has become nervous without other signs; an ataxic animal that is easy to handle) makes the clinical diagnosis more difficult. In these cases, testing the response to external stimuli (see tests of hyper-reactivity) may be useful to support the clinical suspicion of BSE: Cattle with BSE are more likely to respond abnormally to at least two of the four tests of hyper-reactivity [15].

Recumbent and casualty slaughter cattle

BSE may be more difficult to diagnose in recumbent cattle because the gait cannot be evaluated and over-reactivity to external stimuli may not be evident, in particular in end-stage disease where cattle may be dull or stuporous [47,48]. In these cases, the clinical history is extremely important because behavioural or locomotor changes may have existed prior to recumbency.

Casualty slaughter cattle often present with recumbency. Any recumbent animal with abnormal positioning of the limbs (see Fig. 3) should be treated as BSE suspect, in particular if they display over-reactivity to external stimuli [49]. Over-reactivity was also an important sign in a model proposed to predict BSE in casualty slaughter cattle [50]: Cattle presenting with at least four of the seven signs aggressiveness, teeth grinding, staring eyes, reduced rumination, recumbency or difficulty getting up and over-reactivity should be regarded as BSE suspects.

Other prion diseases in cattle

Transmission studies of various strains in cattle have been conducted to inform on the disease phenotype generated by the infection. Clinical signs have been described in these studies to provide at least some information about the possible clinical presentation of other prion diseases, which may also apply to unusual BSE cases (H-type or L-type). Studies are currently underway where cattle were inoculated with brains from these BSE cases, and it is expected to see some results in the near future.

Chronic wasting disease in cattle

Intracerebral inoculation of brain suspension from mule deer naturally affected by chronic wasting disease (CWD) resulted in a disease with relatively unspecific clinical signs: weight loss, inappetence and altered behaviour (apprehension or lethargy, aimless circling) and later recumbency [51]. Experimental second passage using brains from affected cattle from the first experiment resulted in similar clinical signs: inappetence, weight loss, dullness, teeth grinding and circling. Although generally unresponsive cattle reacted to loud noises with exaggerated responses, which included collapsing. All affected animals later became recumbent [52].

Transmissible mink encephalopathy in cattle

Three different inocula containing the transmissible mink encephalopathy agent (TME) agent (Hayward, Blackfoot, Stetsonville isolates) were used to challenge calves intracerebrally and produced a disease characterised by apprehension, inappetence, and decreased water consumption. The display of excitability, over-reactivity to auditory stimuli, teeth grinding and nystagmus was more variable. Hypermetria and hind limb ataxia developed in later stages, followed by recumbency. Although the course of the disease was similar for all three inocula, the rate of clinical deterioration appeared faster with the Blackfoot isolate [53]. Another experimental study conducted in the USA several years later to compare first and second passage of TME in cattle by intracerebral inoculation produced a similar disease: Hyperexcitability to unfamiliar objects was displayed to various degrees, sudden falling, low head carriage and aimless circling in the pen was also reported [54].

Scrapie in cattle

Cattle parenterally inoculated with the scrapie agent from sheep or goats (originating from a flock with endemic scrapie in the USA) developed locomotor abnormalities (stilted, stiff gait of the hind limbs, occasionally stumbling and falling and difficulty rising) and dullness with disorientation. Signs usually associated with BSE, such as apprehension or aggressiveness and exaggerated responses to external stimuli, were absent [55]. Similar clinical signs were reported for another study in the USA where cattle were intracerebrally inoculated with a pool of brains from scrapie-affected sheep but most cattle also exhibited inappetence and weight loss [56]. The clinical presentation did not change on second passage in cattle [57]. Other authors reported signs similar to but more subtle than TME in cattle [53].

In the UK, two groups of 10 cattle were intracerebrally inoculated with two temporally separated sources of sheep scrapie, which produced again a disease that was mainly characterised by locomotor abnormalities (ataxia with difficulty rising) and dullness (lowered head, leaning against objects) without over-reactivity to external stimuli. Some cattle were also found lying on the side with their limbs paddling. However, two cattle developed a nervous form of the disease with BSE-like signs, such as nervousness and over-reactivity to external stimuli in addition to ataxia [58].

These studies have shown that cattle can develop prion diseases other than BSE, which can be distinguished from BSE by its clinical, pathological and/or biochemical features. However, it is not known if they could occur naturally since all animals were inoculated by parenteral routes and at least scrapie has so far not been transmissible to cattle by the oral route [59].

It is of importance that not all prion diseases in cattle present with nervousness and over-reactivity, which is generally associated with BSE and often so striking that it can be detected even by someone less familiar with the animal.

The clinical presentation of H-type or L-type BSE is not known yet. If it is similar to some of the experimental diseases mentioned above, where the clinical onset is subtle and the predominant clinical signs are dullness, inappetence and ataxia with difficulty rising and later recumbency, cases will be easily missed by the farmer and simply regarded as “downer cows”.

References

1. Simmons MM, Harris P, Jeffrey M, Meek SC, Blamire IWH, Wells GAH: **BSE in Great Britain: Consistency of the neurohistopathological findings in two random annual samples of clinically suspect cases.** *Vet Rec* 1996, **138**:175-177.
2. Breslin P, McElroy M, Bassett H, Markey B: **Vacuolar lesion profile of BSE in the Republic of Ireland.** *Vet Rec* 2006, **159**:889-890.
3. Gubler E, Hilbe M, Ehrensperger F: **Lesion profiles and gliosis in the brainstem of 135 Swiss cows with bovine spongiform encephalopathy (BSE).** *Schweiz Arch Tierheilkd* 2007, **149**:111-122.
4. Bruce ME, Boyle A, Cousens S, McConnell I, Foster J, Goldmann W, Fraser H: **Strain characterization of natural sheep scrapie and comparison with BSE.** *J Gen Virol* 2002, **83**:695-704.
5. Green R, Horrocks C, Wilkinson A, Hawkins SAC, Ryder SJ: **Primary isolation of encephalopathy agent based on a review the bovine spongiform in mice: Agent definition of 150 transmissions.** *J Comp Pathol* 2005, **132**:117-131.
6. Casalone C, Zanusso G, Acutis P, Ferrari S, Capucci L, Tagliavini F, Monaco S, Caramelli M: **Identification of a second bovine amyloidotic spongiform encephalopathy: Molecular similarities with sporadic Creutzfeldt-Jakob disease.** *Proc Natl Acad Sci U S A* 2004, **101**:3065-3070.
7. Jacobs JG, Langeveld JPM, Biacabé A-G, Acutis PL, Polak MP, Gavier-Widen D, Buschmann A, Caramelli M, Casalone C, Mazza M, Groschup M, Erkens JHF, Davidse A, van Zijderveld FG, Baron T: **Molecular discrimination of atypical bovine spongiform encephalopathy strains from a geographical region spanning a wide area in Europe.** *J Clin Microbiol* 2007, **45**:1821-1829.
8. Juling K, Schwarzenbacher H, Williams JL, Fries R: **A major genetic component of BSE susceptibility.** *BMC Biol* 2006, **4**:33.
9. Haase B, Doherr MG, Seuberlich T, Drogemuller C, Dolf G, Nicken P, Schiebel K, Ziegler U, Groschup MH, Zurbriggen A, Leeb T: **PRNP promoter polymorphisms are associated with BSE susceptibility in Swiss and German cattle.** *BMC Genet* 2007, **8**:15.
10. Sauter-Louis C, Clauss M, Chaher E, Klee W, Wichmann HE, Kienzle E: **Breed predisposition for BSE: epidemiological evidence in Bavarian cattle.** *Schweiz Arch Tierheilkd* 2006, **148**:245-250.
11. Saunders GC, Griffiths PC, Cawthraw S, Tout AC, Wiener P, Woolliams JA, Williams JL, Windl O: **Polymorphisms of the prion protein gene coding region in born-after-the-reinforced-ban (BARB) bovine spongiform encephalopathy cattle in Great Britain.** *J Gen Virol* 2007, **88**:1374-1378.
12. Wilesmith JW, Hoinville LJ, Ryan JB, Sayers AR: **Bovine spongiform encephalopathy: aspects of the clinical picture and analyses of possible changes 1986-1990.** *Vet Rec* 1992, **130**:197-201.

13. Austin AR, Simmons MM, Wells GAH: **Pathological temperament changes in bovines.** *Irish Vet J* 1997, **50**:304-&.
14. Braun U, Pusterla N, Schicker E: **Bovine spongiform encephalopathy: Diagnostic approach and clinical findings.** *Comp Cont Educ Pract Vet* 1998, **20**:S270-S278.
15. Konold T, Bone G, Ryder S, Hawkins SAC, Courtin F, Berthelin-Baker C: **Clinical findings in 78 suspected cases of bovine spongiform encephalopathy in Great Britain.** *Vet Rec* 2004, **155**:659-666.
16. Wilesmith JW, Wells GA, Cranwell MP, Ryan JB: **Bovine spongiform encephalopathy: epidemiological studies.** *Vet Rec* 1988, **123**:638-644.
17. Cazeau G, Ducrot C, Morignat E, Lauvergne N, Philippe S, Cohen C, Calavas D: **Surveillance clinique de l'ESB en France - Étude quantitative des caractéristiques des animaux et des signes cliniques observés en cas de suspicion [Clinical surveillance of BSE in France - Quantitative analysis of animal features and clinical signs].** *Rev Méd Vét* 2002, **153**:785-794.
18. Collin E: **Troubles nerveux chez des bovins et ESB.** *Point Vét* 2002, **33**:40-41.
19. Braun U, Gerspach C, Ryhner T, Hauri S: **Pacing as a clinical sign in cattle with bovine spongiform encephalopathy.** *Vet Rec* 2004, **155**:420-422.
20. McElroy MC, Weavers ED: **Clinical presentation of bovine spongiform encephalopathy in the Republic of Ireland.** *Vet Rec* 2001, **149**:747-748.
21. van Wuijckhuise L, Vellema P, Terbijhe RJ: **BSE: klinische diagnostiek en veldervaringen [BSE: clinical diagnosis and field experience.].** *Tijdschr Diergeneeskde* 2001, **126**:279-281.
22. Austin AR, Pawson L, Meek S, Webster S: **Abnormalities of heart rate and rhythm in bovine spongiform encephalopathy.** *Vet Rec* 1997, **141**:352-357.
23. Braun U, Abgottspon S, Gubler E, Schweizer T: **Decreased sedation by xylazine and high blood pressure in cows with BSE.** *Vet Rec* 1999, **144**:715-717.
24. Austin AR, Simmons MM: **Reduced rumination in bovine spongiform encephalopathy and scrapie.** *Vet Rec* 1993, **132**:324-325.
25. Austin AR, Hawkins SAC, Kelay NS, Simmons MM: **New observations on the clinical signs of BSE and scrapie.** In *Transmissible spongiform encephalopathies. Proceedings of a consultation on BSE with the Scientific Veterinary Committee of the Commission of the European Communities: 14-15 September 1993; Brussels.* Edited by Bradley R, Marchant B. Brussels: European Commission, Agriculture; 1994:277-287.
26. Scott PR, Aldridge BM, Clarke M, Will RG: **Cerebrospinal fluid studies in normal cows and cases of bovine spongiform encephalopathy.** *Br Vet J* 1990, **146**:88-90.
27. Scott PR: **Indications for lumbosacral cerebrospinal fluid collection in ruminant species in field situations.** *Agri-Practice* 1996, **17**:30-34.

28. Braun U, Schicker E, Pusterla N, Schönmann M: **Klinische Befunde bei 50 Kühen mit boviner spongiformer Enzephalopathie (BSE) [Clinical findings in 50 cows with bovine spongiform encephalopathy (BSE)].** *Berl Münch Tierärztl Wochenschr* 1998, **111**:27-32.
29. Moorby JM, Dhanoa MS, Austin AR: **Aspects of the metabolism of dairy cows during the incubation of bovine spongiform encephalopathy.** *Vet Rec* 2000, **147**:409-412.
30. Moorby JM, Begley P, Nash RJ, Theodorou MK, Austin AR: **Plasma metabolites indicate energy metabolism disruption during the preclinical phase of bovine spongiform encephalopathy infection.** *Res Vet Sci* 2002, **73**:191-193.
31. Hesketh S, Sassoan J, Knight R, Hopkins J, Brown DR: **Elevated manganese levels in blood and central nervous system occur before onset of clinical signs in scrapie and bovine spongiform encephalopathy.** *J Anim Sci* 2007, **85**:1596-1609.
32. Robey WG, Jackson R, Walters RL, Brackett JM, Harrington CA, Killian WR: **Use of cerebrospinal fluid levels of 14-3-3 in predicting neurodegeneration in confirmed BSE symptomatic cattle.** *Vet Rec* 1998, **143**:50-51.
33. Green AJE, Jackman R, Marshall TA, Thompson EJ: **Increased S-100b in the cerebrospinal fluid of some cattle with bovine spongiform encephalopathy.** *Vet Rec* 1999, **145**:107-109.
34. Riond JL, Hartmann P, Joller-Jemelka HI, Braun U: **S-100 and bovine spongiform encephalopathy.** *Vet Rec* 1999, **145**:114-115.
35. Jones V, Martin TC, Keyes P, Dawson M: **Protein markers in cerebrospinal fluid from BSE-affected cattle.** *Vet Rec* 1996, **139**:360-363.
36. Parveen I, Moorby J, Allison G, Jackman R: **The use of non-prion biomarkers for the diagnosis of Transmissible Spongiform Encephalopathies in the live animal.** *Vet Res* 2005, **36**:665-683.
37. EFSA: **Scientific Report of the European Food Safety Authority on Transmissible Spongiform Encephalopathy (TSE) on a request from the European Commission on the evaluation of a rapid ante mortem BSE test.** *EFSA J* 2006, 1-14.
38. Scott PR: **Detailed neurological examination of suspect cases of bovine spongiform encephalopathy (BSE).** *PhD Thesis.* University of Edinburgh; 1990.
39. Little CJ, Julu PO, Hansen S, Mellor DJ, Milne MH, Barrett DC: **Measurement of cardiac vagal tone in cattle: a possible aid to the diagnosis of BSE.** *Vet Rec* 1996, **139**:527-528.
40. Pomfrett CJD, Glover DG, Bollen BG, Pollard BJ: **Perturbation of heart rate variability in cattle fed BSE-infected material.** *Vet Rec* 2004, **154**:687-691.
41. Barlow R: **Differential diagnosis of bovine neurological disorders.** *In Pract* 1989, **11**:64-73.

42. Wells GA, Sayers AR, Wilesmith JW: **Clinical and epidemiological correlates of the neurohistology of cases of histologically unconfirmed, clinically suspect bovine spongiform encephalopathy.** *Vet Rec* 1995, **136**:211-216.
43. Saegerman C, Claes L, Dewaele A, Desmecht D, Rollin F, Hamoir J, Gustin P, Czaplicki G, Bughin J, Wullepit J, Laureyns J, Roels S, Berkvens D, Vanopdenbosch E, Thiry E: **Differential diagnosis of neurologically expressed disorders in Western European cattle.** *Rev Sci Tech* 2003, **22**:83-82.
44. Nowotni A, Wendel H, Klee W: **Klinische Untersuchung von Rindern auf BSE an einem Vieh- und Schlachthof. [Pre-slaughtering screening of cattle for clinical signs of BSE].** *Dtsch Tierarztl Wochenschr* 2004, **111**:5-7.
45. Saegerman C, Speybroeck N, Roels S, Vanopdenbosch E, Thiry E, Berkvens D: **Decision support tools for clinical diagnosis of disease in cows with suspected bovine spongiform encephalopathy.** *J Clin Microbiol* 2004, **42**:172-178.
46. Braun U, Schicker E, Hörnlmann B: **Diagnostic reliability of clinical signs in cows with suspected bovine spongiform encephalopathy.** *Vet Rec* 1998, **143**:101-105.
47. Collin E: **Étude épidémiologique et clinique des cas de suspicions d'ESB en Côtes d'Armor.** *Bull Group Tech Vét* 2000, **9**:195-200.
48. Braun U, Hauri S, Kihm U, Ehrensperger F: **Evaluation des BSE-Checks bei weiteren 53 Kühen mit BSE [Evaluation of a clinical examination specifically designed to detect bovine spongiform encephalopathy].** *Tierärztl Prax Ausg G Grosstiere Nutztiere* 2007, **35**:111-116.
49. Konold T, Sivam SK, Ryan J, Gubbins S, Laven R, Howe MJ: **Analysis of clinical signs associated with bovine spongiform encephalopathy in casualty slaughter cattle.** *Vet J* 2006, **171**:438-444.
50. Hett AR, Rüfenacht J, Perler L, Heim D: **Eine Methode zur Erkennung von BSE-Verdachtsfällen in der Gruppe der krankgeschlachteten Rinder während der ante mortem Untersuchung [A method to identify BSE suspects in emergency slaughtered cattle during ante mortem examination].** *Schweiz Arch Tierheilkd* 2002, **144**:654-662.
51. Hamir AN, Kunkle RA, Cutlip RC, Miller JM, O'Rourke KI, Williams ES, Miller MW, Stack MJ, Chaplin MJ, Richt JA: **Experimental transmission of chronic wasting disease agent from mule deer to cattle by the intracerebral route.** *J Vet Diagn Invest* 2005, **17**:276-281.
52. Hamir AN, Kunkle RA, Miller JM, Greenlee JJ, Richt JA: **Experimental second passage of chronic wasting disease (CWD(mule deer)) agent to cattle.** *J Comp Pathol* 2006, **134**:63-69.
53. Robinson MM, Hadlow WJ, Knowles DP, Huff TP, Lacy PA, Marsh RF, Gorham JR: **Experimental infection of cattle with the agents of transmissible mink encephalopathy and scrapie.** *J Comp Pathol* 1995, **113**:241-251.
54. Hamir AN, Kunkle RA, Miller JM, Bartz JC, Richt JA: **First and second cattle passage of transmissible mink encephalopathy by intracerebral inoculation.** *Vet Pathol* 2006, **43**:118-126.

55. Clark WW, Hourrigan JL, Hadlow WJ: **Encephalopathy in cattle experimentally infected with the scrapie agent.** *Am J Vet Res* 1995, **56**:606-612.
56. Cutlip RC, Miller JM, Race RE, Jenny AL, Katz JB, Lehmkuhl HD, Debey BM, Robinson MM: **Intracerebral transmission of scrapie to cattle.** *J Infect Dis* 1994, **169**:814-820.
57. Cutlip RC, Miller JM, Lehmkuhl HD: **Second passage of a US scrapie agent in cattle.** *J Comp Pathol* 1997, **117**:271-275.
58. Konold T, Lee YH, Stack MJ, Horrocks C, Green RB, Chaplin M, Simmons MM, Hawkins SA, Lockey R, Spiropoulos J, Wilesmith JW, Wells GA: **Different prion disease phenotypes result from inoculation of cattle with two temporally separated sources of sheep scrapie from Great Britain.** *BMC Vet Res* 2006, **2**:31.
59. Cutlip RC, Miller JM, Hamir AN, Peters J, Robinson MM, Jenny AL, Lehmkuhl HD, Taylor WD, Bisplinghoff FD: **Resistance of cattle to scrapie by the oral route.** *Can J Vet Res* 2001, **65**:131-132.