BJVP
Brazilian Journal of Veterinary Pathology
ISSN 1983-0246

Review Article

What is an Atypical BSE?

Antonio C. Alessi[1*]

[1] Unesp – São Paulo State University, Dept. of Veterinary Pathology., Unesp, Jaboticabal, SP, Brazil.
*** Corresponding Author:** Via de acesso Prof. Paulo Donato Castellane, s/n, Jaboticabal, SP 14884-900, Brasil. E-mail: antonio.alessi@gmail.com

Submitted September 17th 2013, Accepted October 25th 2012

Abstract

The number of cases of Bovine Spongiform Encephalopathy (BSE) in the United Kingdom (UK) and Europe has decreased during the last years. The disease is designated as Classical BSE (C-BSE) once the prion protein involved is very constant and has genetic identity. On the other hand, atypical cases have occurred in several countries, apparently without any relationship with contaminated feeding. Atypical cases, H or L-BSE can have involvement with the etiology of the known C-BSE, first diagnosed in the UK. With the control of C-BSE based on rigid control of feeding, the occurrence of atypical BSE may predominate in the future. In this hypothesis atypical BSE, probably a spontaneous encephalopathy of cattle, will be considered as Sporadic BSE in contrast with the C-BSE that could be nominated UK-BSE.
Key Words: Bovine Spongiform Encephalopathy, BSE, Atypical BSE, cattle, prion protein.

Introduction

The history of unconventional virally induced encephalopathies started to change dramatically when Wells et al., 1987 (37) communicated the diagnosis of a novel spongiform encephalopathy in cattle. This disease was associated with a novel neurological clinical syndrome characterized by relative constancy of signals, insidious onset and progressive course necessitating slaughter in one to six months. The cases started in April 1985 and were observed only in Friesian/Holstein cattle, aged between three and six years, from dairy herds in widely separated geographical locations of England. The authors suggested the provisional designation Bovine Spongiform Encephalopathy (BSE) for the disorder. The very elegant short communication was published in the Veterinary Record, showing histological aspects of the intriguing disease, very similar to the known spongiform encephalopathies of humans, sheep, goats, captive mule deer, rocky mountain elk and ranch reared mink. Vacuolation of grey matter neuropil and vacuoles in neuronal perikaryon were the most characteristic aspects observed on histological examination. This vacuolation varied in severity with anatomic location but the pattern of variation was similar in different animals. Necrotic neurons were also occasionally observed. Fibrils appeared in the ultra-structural analysis of fresh brain tissue from affected cows.

The epidemiological studies were developed in the following months and published by Wilesmith et al., 1988 (39). A wide collection of data was assessed. No chemical substances could be implicated as well vaccines or hormones, and no newly introduced animals were a common factor in the farms with clinical cases. Finally it was suggested that exposure of cattle to a scrapie-like agent, via cattle feedstuffs containing ruminant-derived protein, beginning in the 1981/82 years was involved. During the following years the number of cases increased (29) as an epidemical occurrence (Fig. 1). In 1992 the number of reported cases reached more than 35000 cases, decreasing in the next years. In 2010, 2011 and 2012 the number of cases respectively reported were 11, 7 and 3. The control of the disease started with a feed ban (ruminants protein forbidden to ruminants) in 1988 (38), reinforced in 1996 (animal protein forbidden to ruminants). This measure was necessary because very low doses of infective material can infect cattle by the oral pathway (36). In 1996 researcher groups had strong evidence that BSE was the cause of a new human disease named variant Creutzfeldt-Jakob Disease (vCJD) (40).

C-BSE cases occurred in many other countries in Europe (Fig. 2) (29) due to the import of animals and food from the UK. The number of cases in Ireland, Portugal and France was greater than one thousand that means much lower than in the UK where the total diagnosed cattle reached 184,621 by 2012. This represents 97% of all European cases. On the other hand the number of cases in Europe greatly decreased in the last years. During the period 2010-2012 the number of cases in Spain reached 25, comparable with the 21 cases diagnosed in the UK. The remaining countries had lower number of cases (Fig. 3). Autochthonous BSE cases were diagnosed also in countries outside Europe, including Canada (total of 20 cases), USA (total of 3 cases), Japan (total of 36 cases), Israel (one case) and Brazil (one case). Some of the cases were detected during the screening in the abattoir or in imported animals (29).

Origin of BSE

The theories about the origin of the BSE agent were concentrated in the scrapie agent at first, but evidences were not convincing (21, 12). For example, intracerebral inoculation of scrapie in transgenic mice induces an encephalopathy with clinical onset and neuropathological changes different from those caused by inoculation of BSE or vCJD (21). Another theory about the origin of BSE agent was based on the hypothesis that wild animals dead in the zoos could be introduced in the animal feeding in the UK. Dead animals of the zoos usually were sent to meat and bone processing plants. Because of this, wild Bovidae, Felidae or African antelope were pointed as possible sources of infection once they could be carrying an undiagnosed sporadic spongiform encephalopathy. The evidence for this theory has not been supported (21). The human origin for the BSE epidemic in the UK was presented by Colchester & Colchester, 2005 (12). Humans remains present in imported mammalian raw material introduced in the feeding of animals could have contaminated cattle. No further evidence of this theory was presented. Currently the intrinsic theory has gained strength, because of the description of atypical forms of BSE, not linked to contamination via food. The origin of BSE could have been intrinsic, arising spontaneously in individual cattle. This admits that a natural rare Transmissible Spongiform Encephalopathy (TSE) in cattle occurs, probably in many countries and it could have been introduced in the feeding of cattle in the UK (4).

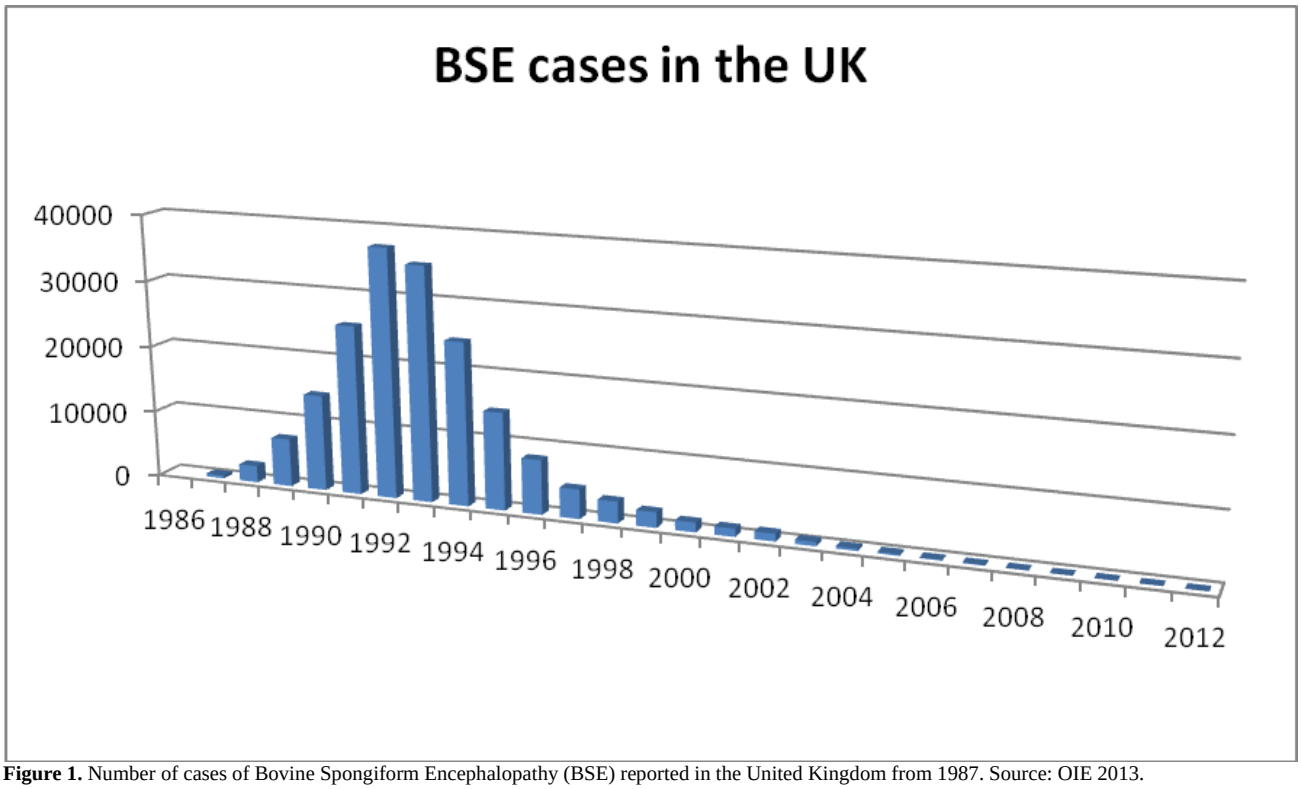

Figure 1. Number of cases of Bovine Spongiform Encephalopathy (BSE) reported in the United Kingdom from 1987. Source: OIE 2013.

The prion hypothesis

The etiology of scrapie was studied by many authors in the past (2, 22, 44). New studies on the etiologic agent of scrapie were in development early in the 1980s. Prusiner (1982) presented a new concept of infective protein – the prion hypothesis (24, 31). A very innovative concept that was thoroughly tested and contested (1, 27, 28) for many years. The detailed history of the prion was presented recently by Liberski (21). The prion hypothesis had been extended to cover other neurodegenerations besides

scrapie. The diseases included in the group of TSEs – the term adopted currently- that affects humans are kuru (17), Creutzfeldt-Jakob disease (CJD) (18), Gerstmann-Sträussler-Scheinker (GSS) syndrome (23), and fatal familial insomnia (25, 26). Animal TSEs are natural scrapie in sheep, goats (22, 44) and mouflons (45), transmissible mink encephalopathy in ranch-reared mink (9), chronic wasting disease of mule deer and elk (41, 42), bovine spongiform encephalopathy or "mad cow disease" (6, 7, 13, 37) and its analogues in several exotic species of antelopes (14, 16, 19, 20) and wild felids in zoological gardens (43), and feline spongiform encephalopathy in domestic cats (46). TSE pathogenesis involves the modification of a normal cellular protein PrPc into a pathogenic form designated PrPsc (sc from scrapie) or PrPres (res – protease resistant). These chronic diseases are associated with the accumulation of a protease-resistant disease associated isoform of the prion protein (PrPsc) in the central nervous system and other tissues, depending on the species. This structural transition is accompanied by profound changes in the physicochemical properties of the PrP (24, 32).

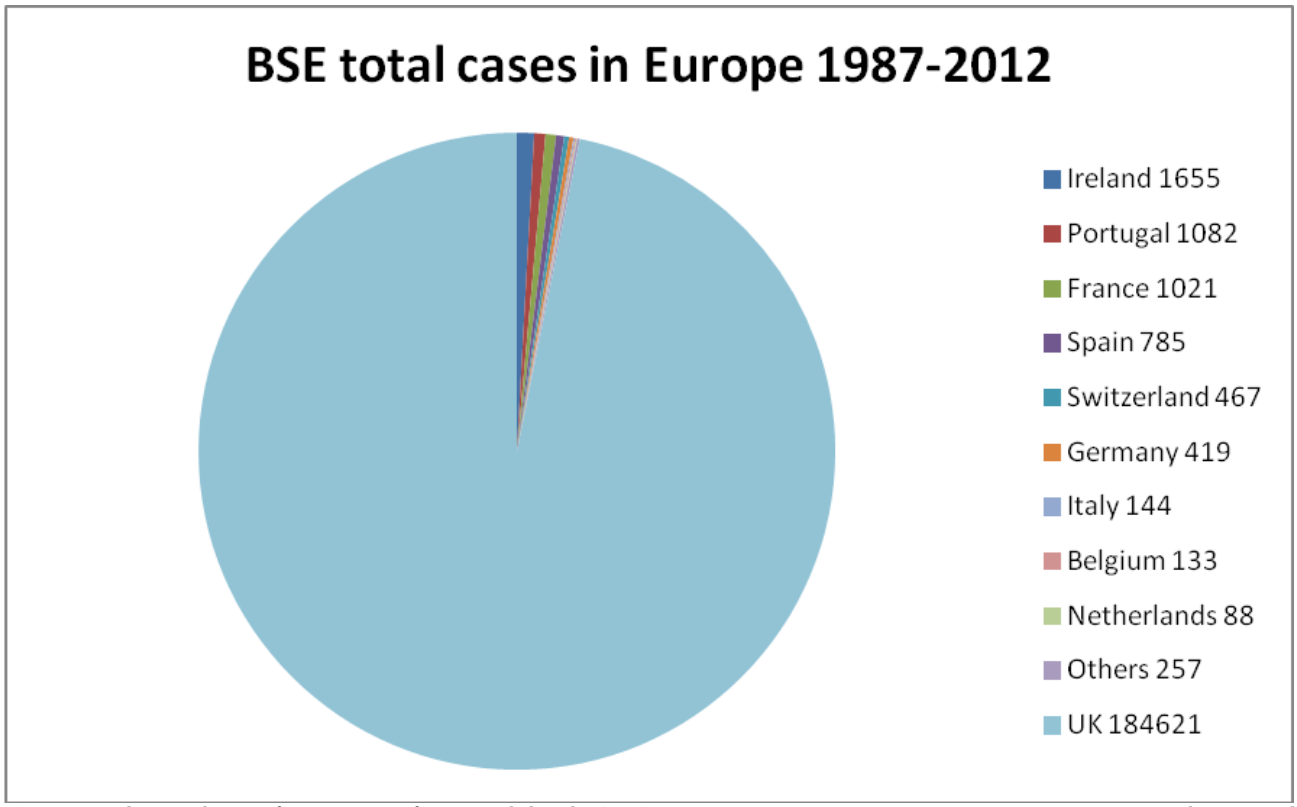

Figure 2. Total reported cases of Bovine Spongiform Encephalopathy (BSE) in European countries. UK cases represent 97%. Spain reports three atypical BSE cases. Switzerland reports one atypical imported BSE case. Source: OIE 2013.

Atypical BSE

Atypical BSE was first described in 2004 in Italy (11) as a novel molecular phenotype in cattle, the L type, in contrast with the C (classic) type of the typical BSE. During the same year a second atypical BSE variant, the H-type, was reported in France (5) and later in Canada, Denmark, Germany (10), Ireland, Italy, Japan, Netherlands, Poland, Sweden, Switzerland, UK (33, 34, 35) and Brazil (3, 8). Belgium analyzed most of the BSE cases and found no atypical case (15). Based on Western Blot (WB) analysis L-type demonstrates faster electrophoretic mobility of PrPSc unglycosylated moiety (5). This type is also called bovine amyloidotic spongiform encephalopathy (BASE) because of the presence of amyloidotic plaques. The H-type cases were characterized by a higher molecular weight of the unglycosylated fraction of PrPSc than C-type BSE. It is acceptable that both types of atypical cases are not originated from the BSE prion that caused the epidemic outbreak in the UK in the decades of 1980 and 1990. The occurrence of atypical cases is supposed to be sporadic (30). On the other hand the emergence of C-BSE strain properties during serial passages of H-BSE in wild-type mice was reported by Baron et al (4). The study sheds light on the origin of the British BSE epizootic disease. The importance of this study (4) refers to the origin of the British epidemic BSE. A conversion of an atypical form into a "classical" form could have occurred. In the near future, it is expected that the control of the disease now denominated C-BSE will reduce drastically the number of cases in all countries. This is evidenced by the data presented nowadays by OIE (29) in contrast with previous

data (Figs. 1-3). On the other hand, the prevalence of "atypical" cases, or Sporadic BSE (S-BSE), is growing as the surveillance includes de immunohistochemical, ELISA, WB and genetic analyses in the diagnosis. The analysis of older cattle is also a condition that should reveal more sporadic cases. Thus, it can be expected that the number of cases of S-BSE will overcome the number of C-BSE.

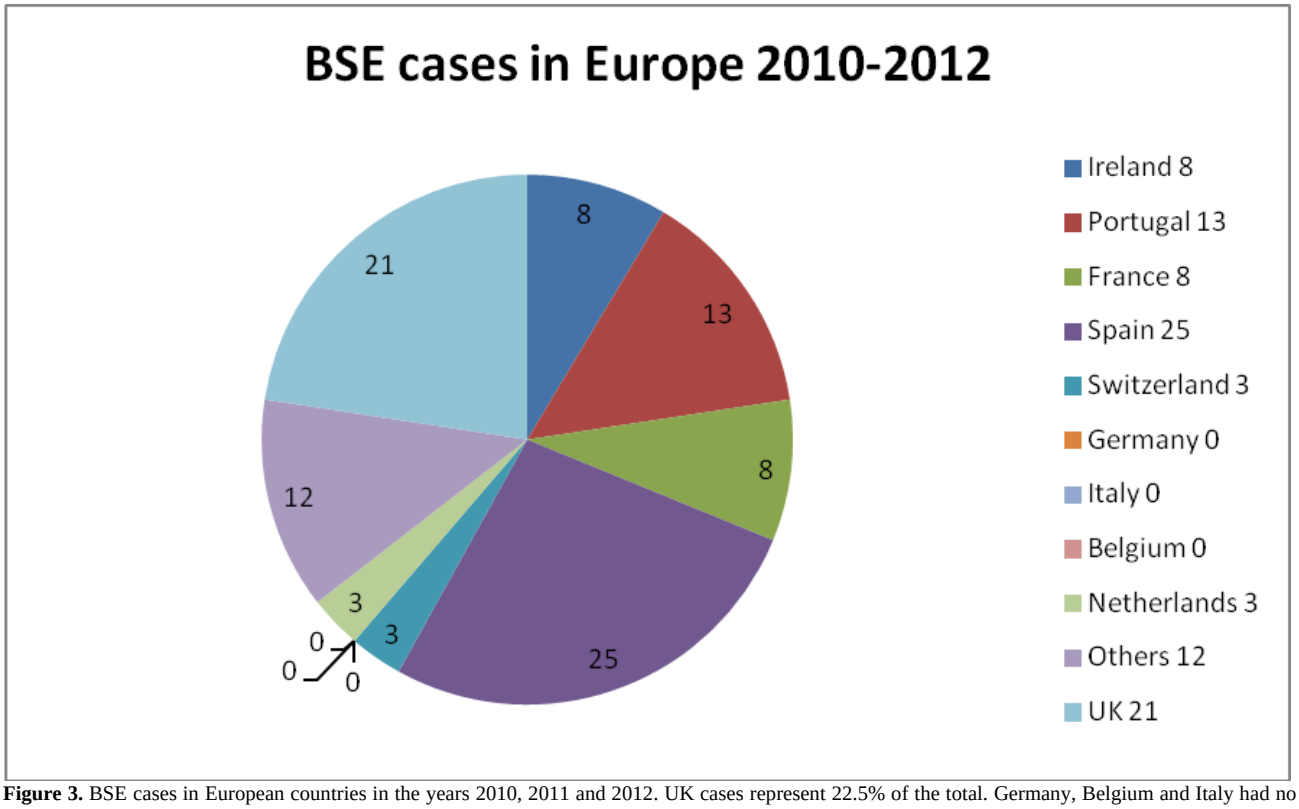

Figure 3. BSE cases in European countries in the years 2010, 2011 and 2012. UK cases represent 22.5% of the total. Germany, Belgium and Italy had no cases in this period. Spain reports three atypical BSE cases. Switzerland reports one atypical imported BSE case. Source: OIE 2013.

Conclusion

With the control of C-BSE based on rigid control of feeding, the occurrence of atypical BSE may predominate in the future. In this hypothesis atypical BSE, probably a spontaneous encephalopathy of cattle, will be considered a sporadic BSE (S-BSE), type H or type L, in contrast with the C-BSE that could be renamed to UK-BSE.

References

1. ADAMS DH. Does the infective agent of scrapie replicate without nucleic acid? An Assessment. **Med. Hypotheses** 1991, 35, 253-264.
2. ADAMS DH. The nature of the scrapie agent. A review of recent progress. **Pathol. Biol.** 1970; 18, 559-577.
3. ALESSI AC. Atypical BSE in Brazil and worldwide. **Braz. J. Vet. Pathol.** 2012, 6, 1-2.
4. BARON T., VULIN J., BIACABE AG., LAKHDAR L., VERCHERE J., TORRES JM., BENCSIK A. Emergence of Classical BSE Strain Properties during Serial Passages of H-BSE in Wild-Type Mice. **PLoS ONE** 2011. 6, e15839. doi:10.1371/journal.pone.0015839.
5. BIACABE AG., LAPLANCHE JL., RYDER S., BARON T. Distinct molecular phenotypes in bovine prion diseases**. EMBO Rep.** 2004, 5,110-115.
6. BRADLEY R, COLLEE JG, LIBERSKI PP. VARIANT CJD (vCJD) and bovine spongiform encephalopathy (BSE): 10 and 20 years on: part 1. **Folia Neuropathol.** 2006; 44, 93-101.
7. BRADLEY R, LIBERSKI PP. Bovine spongiform encephalopathy (BSE): the end of the beginning or the beginning of the end? **Folia Neuropathol.** 2004; 42 Suppl A, 55-68.
8. BRASIL. Ministério da Agricultura, Pecuária e Abastecimento (www.agricultura.gov.br/arq_editor/file/Homepage/Nota%20Oficial%20EEB/Official %20Note%20EBB%20-%2018_12_2012.pdf). Access in 12-02-2012.
9. BURGER D., HARTSOUGH GR. A scrapie-like disease of mink. In **Report of a Scrapie Seminar.** United States Department of Agriculture 1964; paper 27, 225-227.
10. BUSCHMANN A., GRETZSCHEL A., BIACABE A-G., SCHIEBEL K., CORONA C., HOFFMANN C., EIDEN M., BARON T., CASALONE C., GROSCHUP MH. Atypical BSE in Germany - Proof of transmissibility and biochemical characterization. **Vet. Microbiol.** 2006, 117,103-116.
11. CASALONE C., ZANUSSO G., ACUTIS PL., FERRARI S., CAPUCCI L., TAGLIAVINI F., MONACO S., CARAMELLI M. Identification of a second bovine amyloidotic spongiform encephalopathy: molecular similarities with sporadic Creutzfeldt-Jacob disease. **Proc. Natl. Acad. Sci.** USA 2004, 101, 3065-3070.
12. COLCHESTER ACF., COLCHESTER NTH. The origin of bovine spongiform encephalopathy: the human prion disease hypothesis. **Lancet**, 2005, 366, 856-861.
13. COLLEE JG, BRADLEY R, LIBERSKI PP. Variant CJD (vCJD) and bovine spongiform encephalopathy (BSE): 10 and 20 years on: part 2. **Folia Neuropathol.** 2006; 44, 102-110.
14. CUNNINGHAM AA., WELLS GAH., SCOTT AC., KIRKWOOD JK., BARNETT JEF. Transmissible spongiform encephalopathy in greater kudu (Tragelaphus strepsiceros). **Vet. Rec.** 1993, 132, 68.

15. DOBLY A., LANGEVELD J., VAN KEULEN L., RODEGHIERO C., DURAND S., GEEROMS R., VAN MUYLEM P., SLOOVERE J., VANOPDENBOSCH E., ROELS S. No H- and L-type cases in Belgium in cattle diagnosed with bovine spongiform encephalopathy (1999-2008) aging seven years and older. **BMC Vet. Res.** 2010, 6, 26.
16. FLETWOOD AJ., FURLEY CW. Spongiform encephalopathy in an eland. **Vet. Rec.** 1990; 126, 215-222.
17. GAJDUSEK DC., GIBBS CJ., ALPERS MP. Experimental transmission of a kuru-like syndrome to chimpanzees. **Nature** 1966; 209, 794-796.
18. GIBBS CJ. Jr, GAJDUSEK DC., ASHER DM., ALPERS MP., BECK E., DANIEL PM., MATTHEWS WB. Creutzfeldt-Jakob disease (spongiform encephalopathy): transmission to chimpanzee. **Science** 1968; 161, 388-389.
19. JEFFREY M., WELLS GAH. Spongiform encephalopathy in a Nyala (Tragelaphus angasi). **Vet. Pathol.** 1988; 25: 398-399.
20. KIRKWOOD JK., WELLS GAH., CUNNINGHAM AA., JACKSON SI., SCOTT AC., DAWSON M., WILESMITH JW. Scrapie-like encephalopathy in a greater kudu (Tragelaphus strepsiceros) which had not been fed ruminant-derived protein. **Vet. Res.** 1992; 130, 365-367.
21. LIBERSKI PP. Historical overview of prion diseases: a view from afar. **Folia Neuropathol.** 2012, 50, 1-12.
22. M'GOWAN JP. **Investigation into the disease of sheep called "scrapie" (Traberkrankheit, La tremblante).** With especial reference to its association with Sarcosporidiosis. William Blackwood and Sons, Edinburgh, 1914.
23. MASTERS CL., GAJDUSEK DC., GIBBS CJ Jr. Creutzfeldt-Jakob disease virus isolations from the Gerstmann-Straussler syndrome. With an analysis of the various forms of amyloid plaque deposition in the virus induced spongiform encephalopathies**. Brain** 1981, 104, 559-588.
24. MCKINLEY MP., BOLTON DC., PRUSINER SB. A protease resistant protein is a structural component of the scrapie prion. **Cell** 1983, 35, 57-62.
25. MEDORI R., MONTAGNA P., TRITSCHLER H-J., LEBLANC A., CORDELLI P., TINUPER P., LUGARESI E., GAMBETTI P. Fatal familial insomnia: a second kindred with mutation of prion protein gene at codon 178. **Neurology** 1992, 42, 669-671.
26. MEDORI R., TRITSCHLER H-J., LEBLANC A., VILLARE F., MANETTO V., CHEN HY., XUE R., LEAL S., MONTAGNA P., CORTELLI P., TINUPER P., AVONI P., MOCHI M., BARUZZI A., HAUW JJ., OTT J., LUGARESI L., AUTILIO-GAMBETTI L., GAMBETTI P. Fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene**. N. Engl. J. Med.** 1992, 326, 444-449.
27. NARANG H. A critical review of the nature of the spongiform encephalopathy agent: protein theory versus virus theory. **Exp. Biol. Med.** (Maywood), 2002, 227, 4-19.
28. NARANG H. The nature of the scrapie agent: the virus theory. **Proc. Soc. Exp. Biol. Med.** 1996, 212, 208-224.
29. OIE – World Organization for Animal Health. BSE situation in the world and annual incidence rate. http://www.oie.int/en/animal-health-in-the-world/bse-specific-data/. Access in 20/08/2013.
30. PORCARIO C., MARK HALL S., MARTUCCI F., CORONA C., IULINI B., PERAZZINI AZ., ACUTIS P., HAMIR AN., LOIACONO CM., GREENLEE JJ., RICHT JA., CARAMELLI M., CASALONE C. Evaluation of two sets of immunohistochemical and Western blot confirmatory methods in the detection of typical and atypical BSE cases. **BMC Res. Notes** 2011, 4, 376
31. PRUSINER SB. Novel proteinaceous infectious particles cause scrapie. **Science**, 1982, 216, 136-144.
32. PRUSINER SB. Prions. **Proc. Natl. Acad. Sci. USA**, 1998, 95, 13363-13383.
33. RICHT JA., HALL SM. BSE case associated with prion protein gene mutation. **PLoS Pathog.** 2008, 4, 1000156.
34. RICHT JA., KUNKLE RA., ALT D., NICHOLSON EM., HAMIR AN., CZUB S., KLUGE J., DAVIS AJ., HALL SM. Identification and characterization of two bovine spongiform encephalopathy cases diagnosed in the United States. **J. Vet. Diagn. Invest.** 2007, 19, 142-154.
35. STACK MJ., FOCOSI-SNYMAN R., CAWTHRAW S., DAVIS L., CHAPLIN MJ., BURKE PJ. Third atypical BSE case in Great Britain with an H-type molecular profile. **Vet. Rec.** 2009, 165, 605-6.
36. WELLS GAH., KONOLD T., ARNOLD ME., AUSTIN AR., HAWKINS SAC., STACK M., SIMMONS MM., LEE YH. GAVIER-WIDE D., DAWSON M., WILESMITH JW. Bovine spongiform encephalopathy: the effect of oral exposure dose on attack rate and incubation period in cattle**. J. Gen. Virol.** 2007, 88, 1363–1373.
37. WELLS GAH., SCOTT AC., JOHNSON CT., GUNNING RF., HANCOCK RD., JEFFREY M., DAWSON M., BRADLEY R. A novel progressive spongiform encephalopathy in cattle. **Vet. Rec.** 1987; 121: 419-420.
38. 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.
39. WILESMITH JW., WELLS GA., CRANWELL MP., RYAN JB. Bovine Spongiform Encephalopathy: epidemiological studies. **Vet. Rec.** 1988, 123, 638-44.
40. WILL RG., IRONSIDE JW., ZEIDLER M. A new variant of Creutzfeldt-Jakob disease in the UK. **Lancet** 1996, 347, 921-925.
41. WILLIAMS ES., YOUNG S. Chronic wasting disease of captive mule deer: a spongiform encephalopathy. **J. Wildlife Dis.** 1980, 16, 89-98.
42. WILLIAMS ES., YOUNG S. Spongiform encephalopathy in a Rocky Mountain elk. **J. Wildlife Dis.** 1982, 18, 465-471.
43. WILLOUGHBY K., KELLY DF., LYEON DG., WELLS GAH. Spongiform encephalopathy in a captive puma (Felis concolor). **Vet. Res.** 1992, 131, 431-434.
44. WILSON DR, RUTH D, ANDERSON RD, SMITH W. Studies in scrapie. **J. Comp. Pathol.** 1950, 60, 267-282.
45. WOOD JLN., LUND LJ., DONE SH. The natural occurrence of scrapie in moufflon. **Vet. Rec.** 1991, 130, 25-27.
46. WYATT JM., PEARSON GR., SMERDON TN., GRUFFYDD-JONES TJ., WELLS GA., WILESMITH JW. Naturally occurring scrapie-like spongiform encephalopathy in five domestic cats. **Vet. Rec.** 1991, 129, 233-236.