RETROSPECTIVE COHORT STUDY OF RUMINANTS WITH NEUROLOGICAL DISORDERS

L. Giles; J. Orr BMVS MRCVS; J. Guevar DVM MRCVS; L. Viora MVB, Dip. ECBHM MRCVS; R. Gutierrez-Quintana MVZ MVM DipECVN MRCVS; D. Logue BVMS PhD FRCVS;

Corresponding author: julien.guevar@gmail.com

Key words: Neurology, Prevalence, Bovine, Ovine, Differential Diagnosis

Abstract

This study reports the neurological disease cases donated to the Scottish Centre for Production Animal Health and Food Safety (SCPAHFS), University of Glasgow, by veterinarians in the field. It gives a different insight into the pattern of neurological diseases in ruminants than that presented by Veterinary Investigation Diagnosis Analysis database (VIDA). Between January 2006 and June 2016, 96 ruminants presented with neurological signs. Forty-seven different neurological presenting signs were reported with 79% of the donated patients presenting with abnormal gait. Calves were significantly more likely to present with neurological signs than adult cattle, when compared to the ratio of calves to adults in the Scottish cattle population. This was not the case for sheep. Lesions were most commonly localized to the spinal cord in sheep 44.1% (15 cases), the peripheral nervous system in cattle 45.9% (28 cases) and to the brain in the overall population 41.1% (39 cases). The aetiology of 38% of pathologies observed was idiopathic (36 cases), making this the most common cause of ruminant neurological disease in this study. Neurological diagnoses were reached in 84% of patients, with 28 different diagnoses made. The most frequently diagnosed conditions in ruminants over the ten years were spastic paresis, vertebral oesteomyleitis and listeriosis.

Introduction

Scanning surveillance of veterinary diseases in Scotland has recently been reviewed and reported as imperfect (Anon 2011). The Veterinary Investigation Diagnosis Analysis database (VIDA) records and reports data from veterinary laboratories in Great Britain (GB) and is currently the main source of passive surveillance information in GB. Between 2007 and 2014, the majority of animals within the 'Neurological Disease' VIDA category fell into the group "Diagnosis not reached – nervous disease" (77.4% in cattle, 35.2% of sheep).

Neurological conditions in cattle and sheep are particularly relevant as indicators of toxicity, possible zoonotic diseases and are also associated with pain and distress, having a significant effect on productivity and animal welfare (Vlamynck and others 2014; Constable 2004; Anon 1996). Neurological disorders in livestock have proven to be notoriously difficult to classify, diagnose and treat (Saegerman and others, 2003; Finnie and others, 2011). The aim of this retrospective cohort study was to collate and report on the ruminant cases presented to the University of Glasgow teaching hospital with neurological disorders over a ten year period.

Materials and Methods

The Scottish Centre for Production Animal Health and Food Safety (SCPAHFS)

SCPAHFS is the teaching facility for production animals at the School of Veterinary Medicine, University of Glasgow. The majority of cases come from a tight band of farms in Scotland, coast to coast, from Perth (North) to Stranraer (South) - a catchment of approximately half a million cattle, including youngstock and two million sheep, including lambs (Anon 2016). The cases seen are donated via first opinion practice veterinarians, who perform an initial clinical assessment and determine that the animals are fit for transport to the centre. All cases are admitted as donations and become the property of the University of Glasgow. Farmers receive a small monetary gesture of gratitude and both the vet and farmer receive feedback on the case progression and outcome.

SCPAHFS has taken the decision that accepting farm animal referral cases into the centre with an aim of recovery and return is not ethical and has considerable biosecurity risks given the occasional presence of diseases such as Johne's, Infectious Bovine Rhinotracheitis (IBR) and persistent Bovine Viral Diarrhoea Virus (BVDV) infection. In a few instances (eight individuals during the period of study) recovered cases were allowed to be returned to their farm of origin after discussion with the owner and his veterinarian about the disease risks of such a return. After a clinical assessment upon admission, a decision is made to progress to further diagnostics and/or treatment, or to euthanise the animal and send it for *post mortem* examination. If appropriate in terms of welfare of the animal, some may remain in the clinic for further student teaching. These individuals are evaluated regularly and sent for *post mortem* when appropriate. In both situations the *post mortem* allows a more accurate diagnosis and facilitates anatomical pathology teaching. Since the animal will always be subjected to *post mortem*, some of the more invasive neurological techniques (such as a cerebrospinal tap) are rarely undertaken in the live animal.

*Study populatio*n

This was a retrospective cohort study; the medical records of all ruminants donated to SCPAHFS for a nervous system abnormality during the time period January 2006 to June 2016 were identified from the hospital computer database and selected for further review. Ruminants were included in the study if sufficient information was available in the clinical records to verify that they had a disease of the nervous system. During this period of time a total of 1,765 ruminants were donated to the hospital, and 96 of them fitted the criteria for inclusion in this study.

For each case the following information was recorded: age, sex, species, breed, presenting complaint, duration of clinical signs, clinical and neurological examination findings at presentation, ancillary test(s) results, case progression, presumptive clinical diagnosis, PM examination findings (if available) and definitive diagnosis (if reached). Duration of condition at time of presentation was defined as: acute <1 day, subacute < 1 week, chronic >1 week (Blood and others 2006). The progression of cases was classified as: recovered, static, euthanised due to welfare concerns or died. Static cases were defined as those that did not recover but were deemed “stable”, being able to manage essentially normally (able to stand, lie down, move, feed etc.,) in a single pen with sight and touch to some of their peers

A neurological examination form was available to record the findings during the examination of patients. As part of this study, the recorded neurological signs were grouped into ten categories (as they would be in a chronological neurological assessment): mentation, behaviour, gait, posture, balance, proprioception, spinal reflexes and musculature, cranial nerve signs, definite or possible cranial nerve involvement and pain signaling. These categories were adapted from the ruminant neurological exam described by PD Constable (Constable 2004). In some instances, cases presenting with neurological signs were examined by board certified veterinary neurologist and/or a resident in veterinary neurology. During this study, if a definitive diagnosis was not immediately clear given the available data, these specialists also reviewed the case.

Available data for each case generally allowed localisation of the lesion(s) to the brain (including forebrain, cerebellum and brainstem), spinal cord or peripheral nervous system. Conditions were also grouped by aetiology into the VITAMIN D classification of Jaggy

(2005) (V: vascular, I: inflammatory/infectious, T: trauma, A: anomaly, M: metabolic/toxic, I: idiopathic, N: neoplasia and D: degenerative).

For the purpose of comparing age data in this study to published annual census statistics (Anon 2015), cases from 2016 (four sheep and four cattle) were excluded to match our time frame to theirs. A 95% confidence interval (CI) was calculated for the proportion of ruminants under one-year-old (calves/lambs) presenting to SCPAHFS. This was compared to the average proportion of calves/lambs in the Scottish cattle and sheep population over the same time period. All further descriptive statistical analyses with the full data set were performed using commercially available software (Excel 2016).

Results

The 96 ruminant cases studied represented 5.4% of the total cases admitted to SCPAHFS between January 2006 and June 2016. Sixty-two were cattle and 34 were sheep, no other ruminant species were donated. The median age for all ruminants was seven months, for cattle eight months (range 0-178 months) and for sheep six months (range 0 – 84 months). The proportion of cattle under one-year-old (calves) presenting with neurological signs to SCPAHFS between 2006-2015 was 63.8% (95% CI, 51.4% - 76.2%). The proportion of calves in the Scottish cattle population within this time frame was just under 30%. Therefore, a significantly higher proportion of calves were presented to SCPAHFS for neurological disorders than the proportion of calves in the Scottish cattle population. The proportion of sheep under one-year-old (lambs) presenting to SCPAHFS for neurological signs between 2006-2015 was 60% (95% CI, 42.5% - 77.5%). In the Scottish sheep population, the average proportion of lambs for the same time period was not significantly different, at 48.6%.

Sixty percent of all ruminant cases were female (69% of cattle, 53% of sheep). Eleven different sheep breeds were recorded; the most frequent breed was the Texel. Fourteen cattle breeds were recorded; Holstein Friesian and Holstein Friesian cross were the most prevalent.

The median duration of the clinical signs by the time of presentation at SCPAHFS was seven weeks (range: 0- 84 weeks): 28% of neurological conditions were present from birth (cattle: 33%, sheep: 18%), 4% presented acutely, 12% were sub-acute and 56% were chronic presentations (cattle: 54%, sheep: 61%).

The presenting neurological signs (categorised) on arrival are shown in Figure 1. Seventy-nine percent of cases presented with an abnormal gait and 53% had ataxia. Nineteen percent of cases displayed loss of normal proprioception. Abnormal cranial nerve signs were observed in 32% cases, with bilateral blindness observed in 14%. Eighty-nine percent of the animals had more than one neurological category affected (out of ten).

Case progression was recorded in all but three patients: 58% of cases were euthanized on welfare grounds or died and 42% became static (of which 8% fully recovered clinically). The neuro-anatomical localization of the lesions could be defined in all but three cases, and is shown in Figure 2. Peripheral nervous system localization was most common in cattle and spinal cord localization was most common in sheep. When species were combined the brain was the most common lesion localization overall.

The definitive diagnoses are listed in Table 1. In total there were 28 different definitive diagnoses (note that thirteen percent of cases did not reach a definitive diagnosis, despite specialist review). The three most common diagnoses were spastic paresis (the most prevalent cattle diagnosis), vertebral oesteomyelitits (the most prevalent sheep diagnosis) and listeriosis. The six cases of vertebral oesteomyelitis in sheep presented in cases aged between one and ten months old.

Figure 3 displays the aetiology of cases as defined via the VITAMIN D system. Thirty-eight percent of all cases had an idiopathic aetiology (31 cattle and 5 sheep). Twenty-seven percent of cases had inflammatory or infectious aetiology (12 cattle and 14 sheep). There were no cases with vascular or neoplastic aetiology. Eighteen percent of sheep cases had metabolic/toxic aetiology, and no cattle cases fell into this group. Fourteen percent of cattle disorders were due to trauma; the cases of femoral nerve paralysis were aged between two and 12 weeks old and three vertebral fractures were seen (in cattle aged two, 18 and 52 months). No sheep cases had this traumatic aetiology.

Discussion

The authors of this study acknowledge that due to the referral conditions certain diagnoses were under-represented (Bartlett and others 2010); SCPAHFS is an environment that creates bias. A different but equally biased population is represented by the current source of national herd statistics, VIDA data. In terms of diagnostic submission reported via VIDA the data represents roughly 0.37% of the cattle population and 0.03% of the sheep population of the UK annually (calculations based on the based on the most recent VIDA statistics – 2015).

Within the ten year period of our study, calves were significantly more likely to present with neurological disease than cattle over a year old, when compared to the proportion seen in the Scottish cattle population. This confirms other reports in the literature that neurological pathologies tend to have a preferential distribution in cattle under one-year-old (Heim and others 1997). However, there was no such trend in presenting age for sheep in this series.

Overall the most common localization of neurological signs in ruminants was to the brain, presumably because of the uncertainty of diagnosis by the first opinion veterinarian. For sheep in particular, older animals may be more frequently referred to government labs as possible spongiform encephalopathies. This could also be a source of bias in our sheep figures (we only diagnosed typical scrapie once). With regards to species-specific lesion localisation, without any similar studies of the lesions to brain, spine or peripheral nerves to compare our results to, we cannot yet conclude if they are representative of the general population e.g. if sheep are truly more predisposed to spinal neuropathies than cattle.

Ataxia was the most frequent presenting neurological sign in this study. Clinicians must bear in mind that in general practice this sign is most commonly related to pain or musculoskeletal disorders in large animals (Mayhew 2009). The difficulties of differentiating between disease of the nervous system and syndromes with a neurological expression has previously been discussed (Saegerman 2003). Therefore, a thorough assessment of the animal is recommended to ensure that the abnormality observed is due to a nervous system defect.

The most common diagnosis in cattle was young animals with spastic paresis. Farm and veterinary prejudice in these cases may be present due to the classical and obvious presentation of the disease processes (Cooper and others 1998; Bartlett 2010). Previously

reported as a rare condition (Ledoux 2001), the lack of substantial epidemiological data on cattle spastic paresis has recently been discussed (Vlamynck and others 2014). The prevalence of this pathology in our study supports the need for a greater understanding of this disease.

Vertebral oesteomyelitis is common in cattle and sheep (Divers 2004); in our study it was the most prevalent diagnosis of sheep presenting with neurological signs. Our cases were all under one-year-old, supporting the evidence that this ailment generally occurs in lambs (Finely 1975; Scott and others 1991). There is currently little research into non-epidural-related vertebral oesteomyelitis (to the authors' knowledge, only two case series are published, containing five and eight lamb cases respectively) and tail docking has been hypothesised as a predisposing factor (Finley 1975; Scott and others 1991).

An idiopathic aetiology was confirmed in over a third of cases, which (in part) reflects the high number of congenital pathologies presented over the period of the study. Neoplastic neurological pathologies are rare in cattle (McGill and others 1993, Heim and others 1997) and production animals do not generally live to an age where neoplastic or degenerative processes have the opportunity to cause disease (Constable 2004; Saegerman 2003). A low prevalence of both these aetiologies is demonstrated in our study, supporting these conclusions and also displaying a limitation of using the VITAMIN D aetiology classification system in livestock (Constable 2004).

Infectious / inflammatory causes were the second most common aetiology in this study. The high prevalence of these causes of neurological conditions in livestock has previously been commented on (Saegerman 2003; Constable 2004). In the only other quantitative retrospective ruminant study of neurological disease (to the authors' knowledge), inflammatory process / infectious agent was the most common aetiology, making up 44% of cases (Gustavo and others 2016). However, this alternate study took place in Brazil; a very different epidemiological environment to Scotland.

Toxic/metabolic aetiologies were over represented in sheep compared to cattle; bracken poisoning and Closantel toxicity were the two toxic conditions seen in this study. Both toxicities to the nervous system have been well reported on in sheep (Van Cauteren and others 1985; Vetter 2009; Hanon and others 2014). In contrast, traumatic conditions were over represented in cattle compared to sheep. Vertebral fractures or nerve paralysis in cattle

accounted for all the trauma cases but no sheep cases had this aetiology. Femoral/tibial nerve paralysis due to trauma has only been reported in cattle, and our results support previous claims that it is most commonly seen in calves (Barlow 1989; Divers 2004). The absence of sheep presenting with spinal fractures confirms a previous a retrospective study of 39 ruminant vertebral trauma cases where again cattle were the primary species affected (Borges 2003).

The breadth of conditions diagnosed in this study (along with the variation in presenting neurological signs) reflects the challenging nature of investigating nervous system disease in ruminants in practice. Further investigation into the prevalence and pathogenesis of both spastic paresis and vertebral oesteomyelitis is required. The analysis and the data base provided by this study will hopefully stimulate further studies into non TSE neurological conditions in livestock in the UK.

Tables

Table 1: Definitive diagnoses reached and prevalence of each within sheep and cattle cases

Definitive Diagnosis	**All % (cases)**	**Cattle % (cases)**	**Sheep % (cases)**
Spastic Paresis	19 (18)	29 (18)	0
Vertebral oesteomyelitis	9 (9)	5 (3)	18 (6)
Listeriosis	8 (8)	10 (6)	6 (2)
Hydrocephalus	5 (5)	8 (5)	0
Encephalitis	5 (5)	3 (2)	9 (3)
Femoral / Tibial Nerve Paralysis	5 (5)	8 (5)	0
Congenital Spinal Deformation	3 (3)	0	9 (3)
Spinal Fracture	3 (3)	5 (3)	0
Compressive Cervical Myelopathy	2 (2)	0	6 (2)
Closantel Toxicity	2 (2)	0	6 (2)
Bracken Poisoning	2 (2)	0	6 (2)
Polioencephalomyelitis	2 (2)	3 (2)	0
Cerebellar Hypoplasia	2 (2)	3 (2)	0
Others (<1.5% each)	16 (15)	13 (8)	21 (7)
Diagnosis Not Reached	16 (15)	13 (8)	21 (7)

Other Diagnoses (<1.5% each): **Cattle**: Brain stem lesion, idiopathic nystagmus, microphtalmia, myositis, polymyelia, syringohydromyelia, traumatic neuropraxia, ventriculitis. **Sheep:** Birth asphyxia, brain abscess, cerebrocorticonecrosis, discospondylitis, hepatic encephalopathy, myelomalacia, transmissible spongiform encephalopathy.

Figures

FIG 1 – Frequency of neurological signs at time of presentation (signs are coloured according to category for ease of interpretation)

FIG 2 - Definitive localization of neurological lesion (and species variation)

FIG 3 – Aetiologies of (a) cattle and (b) sheep definitive diagnoses

Acknowledgements

The authors thank all the farmers and veterinarians who donated the patients in our study. Gratitude also goes to Anna Bruguera (for creating the original Excel Spreadsheet of retrospective SCPAHFS cases), Richard Irvine and team for post mortem reports and Rob Kelly for revising our manuscript and lending a mathematical hand.

References

APHA (2015) **Veterinary Investigation Diagnosis Analysis (VIDA) Report 2014** https://www.gov.uk/government/statistics/veterinary-investigation-diagnosis-analysis-vida-report-2014

APHA (2016) **Veterinary Investigation Diagnosis Analysis (VIDA) Report 2015** https://www.gov.uk/government/statistics/veterinary-investigation-diagnosis-analysis-vida-report-2015

BARLOW R. (1989) **Differential diagnosis of cattle neurological disorders** *In Practice* **11** 64-73

BARTLETT, P. C., VAN BUREN, J. W., NETERER, M. & ZHOU, C. (2010) **Disease surveillance and referral bias in the veterinary medical database**. *Preventive Veterinary Medicine* **94**, 264-271

BORGES A.S., SILVA D.P.G., GONCALVES R.C CHIACCHIO S.B., AMORIM R.M., KUCHEMBUCK M.R.G., VULCAN L.C., BANDARRA E.P., LOPES R.S. (2003) **Vertebral fracture in large animals: retrospective study of 39 cases (1987-2002).** *Arquivo Brasileiro de Medicina Veterinária e Zootecnia* **55** 1-3

BLOOD D.C., STUDDERT V.P., GAY C.C. (2006) **Saunders Comprehensive Veterinary Dictionary** 25, 368, 1718

BRUGUERA A, MURDOCH F, MELLOR D, ORR J. (2015) **Usefulness of a teaching farm animal hospital caseload as a source for passive surveillance data**. *Poster presentation at the Association for Veterinary Teaching and Research Work, Royal Veterinary College, September 2015*

CONSTABLE P.D. (2004) **Clinical examination of the ruminant nervous system**. *Veterinary Clinics Food Animal Practice* **20**, 185–214

COOPER J., WALKER R.D. (1998) **Listeriosis**. *Veterinary Clinics of North America: Food Animal Practice* **14,1**. 116-117

DIVERS T.J. (2004) **Acquired spinal cord and peripheral nerve** disease *Veterinary Clinics Food Animal Practice* **20** 231-242

FINLEY G.G. (1975) **A survey of vertebral abscesses in domestic animals in Ontario**. *Canadian Veterinary Journal* **16** 114–7.

FINNIE J.W., WINDSOR P.A., KESSELL A.E. (2011) **Neurological diseases of ruminant livestock in Australia. I: general neurological examination, necropsy procedures and neurological manifestations of systemic disease, trauma and neoplasia**. *Australian Veterinary Journal* **89**, 243-246.

FROOM P., FROOM J. (1992) **Selection bias in using data from one population to another - common pitfalls in the interpretation of medical literature**. *Theoretical Medicine* **13**, 255-259

GUSTAVO Q., PEREIRA P.F.V., AZAMBUJA R., FLAIBAN K.K.M.C., SANTIS G.W., BRACARENSE A.P.F.R.L., HEADLEY S.A., ALFIERI A., LISBÔA J.A.N. (2016) **Differential diagnosis of the bovine neurologic disease in Paraná State, Brazil: between 2009 and 2015**. *Poster presentation at the 29th World Buiatrics Congress, Dublin, Ireland 2016.*

HANNON F.P., ELLIS K.A, GUEVAR J., MARCHESI F., GERAGHTY T., LEACH J.D.G. (2014) **Closantel toxicity in a pregnant ewe at mid gestation: the pathological evaluation of the ewe and lamb nine months later.** *Veterinary Record Case Report* **2, 1**

HEIM D., FATZER R., HORNLIMANN B., VANDEVELDE M. (1997) **Frequency of neurological disease in cattle.** *Schweizer Archiv Tierheilkunde* **139** 354-362

INSTITUTE OF FOOD SCIENCE AND TECHNOLOGY (1996) **BSE: A review of the scientific evidence** *British Food Journal* **98** (**11**) 4-16

JAGGY A. (2005) **Atlas and Textbook of Small Animal Neurology**. 30

LEDOUX J.M. (2001) **Bovine Spastic Paresis: Etiological Hypotheses.** *Medical Hypotheses* **57, 5** 573-579

MAYHEW J. (2009) **Large Animal Neurology 2nd Edition**. 14, 30, 193, 206

MCGILL I.S, WELLS G.A. (1993) **Neuropathological findings in cattle with clinically suspect but histologically unconfirmed bovine spongiform encephalopathy (BSE).** *J. Comp. Pathology* **108,3** 241-260

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. (2003**) Differential diagnosis of neurologically expressed disorders in Western European cattle**. *Rev. Sci Tech.* **22,1** 83-102

SCOTT P.R., PENNY C.D., MURRAY L.D. (1991) **A field study of eight sheep vertebral body abscess cases.** *New Zealand Veterinary Journal* **39**, **3**. 105-107

SCOTTISH GOVERNMENT (2011) **The Review of Veterinary Surveillance Final Report.** 43, 55 http://www.gov.scot/Resource/Doc/362344/0122619.pdf.

SCOTTISH GOVERNMENT (2015) **Results from the 2015 Scottish Agricultural Census**. Appendix of tables. Tables 3 and 4. http://www.gov.scot/ID3/320265

SCOTTISH GOVERNMENT (2016) **'ERSA' – Economic report on Scottish Agriculture** Table C10 (ii) http://www.gov.scot/Publications/2016/06/5559/93

VAN CAUTEREN H, VANDENBERGHE J, HÉRIN V, VANPARYS P, MARSBOOM R. (1985) **Toxicological properties of Closantel** *Drug and Chemical Toxicology* **8, 3**

VETTER J. (2009) **A biological hazard of our age: Bracken fern (Pteridium Aquilinum)– a review** *Acta Veterinaria Hungarica* **57,1** 183-196

VLAMYNCK C., PILLE F., VLAMINCK L. (2014) **Bovine spastic paresis: Current knowledge and scientific voids.** *The Veterinary Journal* **202** 229-235