Horses on pasture may be affected by equine motor neuron disease

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Summary

***Reasons for performing study*: Equine motor neuron disease (EMND) was diagnosed in 3 horses maintained on lush, grass-based pasture. This contrasted with North American studies which identified limited or no access to green herbage as an important risk factor for EMND.**

***Hypothesis*: Grazing horses that have an apparently adequate intake of pasture herbage to meet normal equine vitamin E requirements can develop EMND.**

***Methods*: Owners of 32 European horses diagnosed with EMND completed a questionnaire regarding intrinsic, managemental, nutritional and environmental factors that could potentially be risk factors for EMND, and also regarding clinical signs, treatments and case outcome. Plasma/serum vitamin E data for these horses were supplied by the veterinarians. No control population was studied.**

***Results*: Thirteen of 32 horses (termed the 'grazing' group) had part- or full-time access to grass-based pasture at the onset of EMND (median duration at pasture 12 h/day, range 3–24 h). Five of these horses were at pasture for at least 23.5 h/day at the onset of EMND, 2 of which were at pasture for at least 23.5 h/day throughout the year. Despite grazing, all these horses had a low vitamin E status. The remaining 19 horses resembled those cases reported from North America, in that they had no or limited access to pasture.**

***Conclusions and potential relevance*: A diagnosis of EMND should not be discounted on the basis that a horse has access, even full-time, to lush grass-based pasture. Inadequate vitamin E intake was probably not the sole cause of either the EMND or the low vitamin E status in the grazing horses; the latter was probably the result of abnormal bioavailability or excessive utilisation of vitamin E.**

Introduction

The aetiopathogenesis of equine motor neuron disease (EMND) remains incompletely understood. Consistent with EMND being an oxidative disorder of somatic efferent motor neurons associated with low vitamin E status, affected horses are reported to have no or limited access to green herbage for at least one year. Equine motor neuron disease has also been reproduced by prolonged feeding of a vitamin E deficient diet (Cummings *et al.* 1993; Divers *et al.* 1994; Mohammed *et al.* 1994; DeLaRuaDomenech *et al.* 1995a,b, 1997a,b). Additional risk factors identified in North America include feeding of concentrates and sweet feed, feeding vitamin and mineral mixtures not formulated to provide vitamin E or selenium, geographical location, age, breed, prolonged residence on a premises, history of crib-biting or coprophagia and absence of rabies vaccination (Cummings *et al.* 1993; Mohammed *et al.* 1993, 1994; DeLaRuaDomenech *et al.* 1995a,b, 1997a,b). Since the first report of histopathologically confirmed EMND in Belgium (Sustronck *et al.* 1993), EMND has been identified in many European countries. However, there are no published epidemiological studies of EMND in European horses. This study was prompted by the diagnosis of EMND in 3 British horses that were at pasture. The aims of the study were to 1) survey the grazing history of European EMND-affected horses, 2) compare epidemiological findings and risk factors for EMND in European horses with those reported for North American cases, 3) attempt to identify alternative risk factors for development of EMND in grazing horses and 4) survey clinical signs, treatments and outcome of EMND cases in Europe.

Materials and methods

The study population comprised 32 cases of EMND that occurred in Europe between 1996 and 2004. Cases were included only if EMND had been confirmed histopathologically, either by finding charateristic histopathological changes of neuronal loss at *post mortem* examination or if neurogenic atrophy was evident in biopsies of *type I* fibre predominant muscles (Valentine *et al.* 1998). No control population was studied. Cases were acquired by contacting university and referral clinics throughout Europe. Data were obtained via an owner-based questionnaire regarding subject details, management, environment, clinical signs, treatments and case outcome. The questionnaire was adapted from that used by DeLaRuaDomenech (1997b, Appendix) to identify risk factors for EMND in North America. Plasma/serum vitamin E data were obtained from veterinarians. As vitamin E was assayed in several

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laboratories, variation resulting from interlaboratory differences in methodology cannot be discounted. Plasma/serum vitamin concentrations for horses which had pasture access at the onset of EMND (n = 11) were compared with those for horses which had no pasture access at the onset of EMND (n = 12), and with those previously reported for healthy horses grazing grass-based pastures in Scotland (n = 10) (McGorum *et al.* 2003), using the Mann-Whitney test. The proportions of survivors in the grazing and nongrazing groups were compared using the Chi-squared test. Statistical significance was assumed at 5%.

Results

Horses

Horses originated from Britain (n = 15), Belgium (n = 8), Holland (n = 6), Germany (n = 2) and France (n = 1). Median age at onset was 10 years (range 2–27 years). Breeds/types affected were Warmbloods (34%), British native pony breeds (15%), Thoroughbred and crosses (13%), other miscellaneous breeds of horses (25%) and ponies (13%). There were 16 geldings, 15 mares and one stallion.

Managemental factors

Most cases (n = 29) originated from separate premises; however, 3 originated from one yard following prolonged feeding of a diet lacking fresh herbage. The premises were classified as a livery yard (50%), riding school (21%), farm (14%), field (11%) and stud (4%). Cases had resided on the premises for a median duration of 4 years (range 3 months–10 years). The median duration for which the premises had been used for horses was 11 years (range 4–50 years). Median number of other horses on the premises was 20 (range 1–120). Other animal species were present on most (66%) premises, the most frequent being dogs. No association was found between previous use of the premises (if it was not built specifically for horses) and the presence of EMND cases. No consistent risk factors were identified by analysis of responses relating to the environment within 1.6 km (1 mile) of the premises, although many had close proximity to livestock farms (53%) and power lines (42%). No common potential risk factors were revealed by assessment of pasture factors including mineral deficiencies or excesses, manure collection, application of insecticides, herbicide and fertilisers, crop rotation, grazing of other species and harrowing and reseeding. When indoors, most horses (91%) were housed in a loose-box or stall, while the remainder were group-housed. Analysis of stable construction materials and use of paints did not reveal common potential risk factors. Most horses (75%) were vaccinated regularly, with 71% being vaccinated against influenza and tetanus and one against rabies. Most horses (81%) received regular anthelmintic therapy, consisting of ivermectin (75%), pyrantel (44%), fenbendazole (34%), moxidectin (31%), praziquantel (9%) or mebendazole (9%). There was no common previous medical history or treatment. Of the 12 horses that displayed stable vices, 9 performed coprophagia, 2 wood-chewing and 1 crib-biting.

Nutrition and vitamin E status

Nineteen horses (termed the ‘nongrazing’ group) had no access to pasture at the onset of EMND (Table 1). Of these, 12 horses had no access to grazing throughout the year, while 7 had previously been at pasture for median average durations of 1 h/day (range 0.5–24 h/day) during summer and 1 h/day (range 0–1.5 h/day) during winter. Thirteen horses (the ‘grazing’ group) had access to grazing at the time of onset of EMND (median average duration at pasture 12 h/day, range 3–24 h/day). Five of these horses were at pasture at least 23.5 h/day, 2 of which were at pasture for at least 23.5 h/day throughout the year. In the year prior to onset of EMND, 20 horses had access to grass-based pasture during summer (median duration 7 h/day, range 0.5–24 h/day), while 16 had access to grass-based pasture during winter (2.5 h/day, 0.5–23.5 h/day). Most (94%) cases received concentrates feed, most commonly (63%) comprising complete feed. Twenty-three percent of horses received straight feeds (single dietary ingredients) only, while 9% received only high-fibre pellets. Most horses (84%) received additional forage, consisting of hay (81%), alfalfa (10%), haylage (6%) or silage (3%). Dietary supplements included salt/mineral licks (59%), oil (6%), multivitamins (3%) and biotin (3%).

TABLE 1: Average duration (h/day) of access to pasture at the onset of equine motor neuron disease (EMND) during the summer and winter prior to onset

Case No.	Onset of EMND	Summer	Winter
1*	18	4	2
2*	6	10	6
3*	6	6	6
4*	12	12	0.5
5	0	0	0
6	0	1	1
7	0	0	0
8	0	24	1.5
9	0	3	1.5
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15*	24	24	2
16	0	0	0
17	0	1	0
18*	3	6	3
19	0	0.5	0.5
20	0	0	0
21*	24	24	0
22*	24	24	8
23	0	0	0
24*	5	5	5
25	0	0	0
26	0	0	0
27	0	4	0
28*	8	9	8
29*	23.5	23.5	23.5
30*	23.5	23.5	23.5
31*	8	8	0
32	0	1	1

*Denotes horses that were included in the ‘grazing’ EMND-affected group.

There was no significant difference between serum/plasma vitamin E levels of grazing (median 0.8 mg/l, range 0.4–1.2 mg/l, n = 11) and nongrazing groups (median 0.7 mg/l, range undetectable to 1.5 mg/l, n = 12) (Fig 1). Vitamin E levels of the grazing and nongrazing groups were significantly (P = 0.0001 and 0.0002, respectively) lower than those reported for healthy horses grazing grass-based pastures in Scotland (median 2.5 mg/l, range 2.0–4.4 mg/l) (McGorum *et al.* 2003).

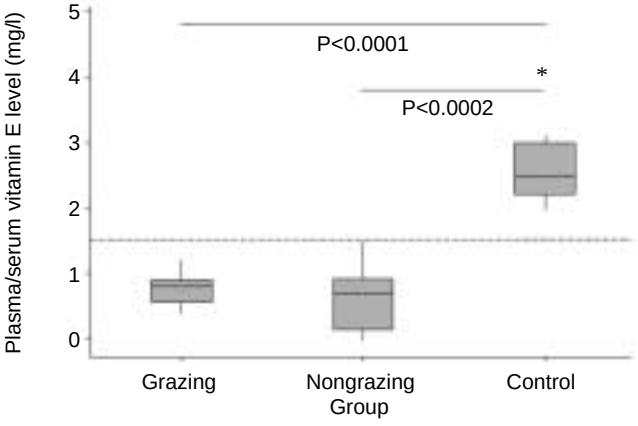

Fig 1: Plasma/serum vitamin E levels for grazing (n = 11) and nongrazing (n = 12) EMND-affected horses and for 10 healthy horses (control) grass-based pastures in Scotland (McGorum et al. *2003). *Statistical outlier. Dashed line = level indicative of deficiency (<1.5 mg/l).*

Clinical signs

Frequencies of owner-reported clinical signs are presented in Table 2.

TABLE 2: Frequency of owner-reported clinical signs in 32 European horses with EMND

Clinical sign	% Horses
Weight loss	91
Atrophy of hindquarters	75
Increased recumbency	75
General weakness	63
Frequent weight shifting	60
Atrophy of back muscles	53
Atrophy of neck muscles	53
Whole body trembling	53
Fine muscle tremors in hindquarters	48
Short gait	43
Low head carriage	43
Fine muscle tremors in forelimbs	38
Excessive sweating	37
Polyphagia	34
Fine muscle tremors in neck	27
Recumbent and unable to rise	26
Fine muscle tremors in back	20
Elevated tail carriage	13
Decreased appetite	12
Atrophy of forelimb muscles	10
Depression and lethargy	8
Hyperaesthesia	4
Anxiety	4

Case management and outcome

Seventy-two percent of horses were treated, predominantly with vitamin E supplementation in varying formulations and dosages (mostly 5000–7000 iu/day). Management changes were made in 41% of horses, mostly consisting of increased access to pasture and change in feed type. An improvement in clinical signs was reported in 45% of treated horses; however, most horses (69%) were subjected to euthanasia because of EMND, with a median duration from diagnosis to euthanasia of 0–3 months (range 0–36 months). At the time of study, the proportion of horses surviving was not significantly higher ($\chi^2 = 1.20$, degrees of freedom = 1, P>0.05) for the grazing group (5/12) than the nongrazing group (3/18). Two horses were subjected to euthanasia for reasons unrelated to EMND.

Discussion

This study was prompted by the authors' diagnosis of EMND in 3 horses that were kept full-time on lush, grass-based pasture. This contrasted with findings of North American studies which identified limited or no access to green herbage as an important risk factor for EMND (Cummings *et al.* 1993; Divers *et al.* 1994; Mohammed *et al.* 1994; DeLaRuaDomenech *et al.* 1995a,b, 1997a,b). In this study, 13 of 32 horses (grazing group) had part- or full-time access to grass-based pasture at the onset of EMND. This indicates that a diagnosis of EMND should not be discounted on the basis of a horse having access, even full-time, to pasture. The 19 nongrazing EMND horses resembled North American cases, since they had no access to pasture at the onset of EMND. As pasture herbage is a rich source of dietary antioxidants, including vitamin E, these nongrazing cases were probably associated, at least partly, with inadequate vitamin E intake. Consistent with this, they all had vitamin E levels indicative of deficiency (<1.5 mg/l; Mayhew *et al.* 1987). In contrast, it is likely that many, if not all, of the 13 grazing horses had a dietary intake of vitamin E that was adequate to meet normal equine requirements, since most pasture grasses supply more than the minimum National Research Council daily estimate of the vitamin E requirement for mature horses (Hintz 1992, 1994; DeLaRuaDomenech *et al.* 1997b). Furthermore, it is stated that vitamin E supplementation is not required for horses that are consuming fresh herbage or grazing pasture (Blakley and Bell 1994). Despite the 13 grazing EMND horses having access to pasture, all had plasma/serum vitamin E levels indicative of deficiency and which were not significantly different from those of nongrazing EMND horses. Vitamin E levels of the grazing EMND group were significantly lower than those previously reported for healthy horses grazing in Scotland. These findings indicate that the duration of access to pasture is not the sole determinant of vitamin E status in EMND-affected horses. One explanation for the low vitamin E status is inadequate intake, due to ingestion of forage with a low vitamin E content. We consider this unlikely since 1) all owners reported that the herbage was typical of pastures used to graze horses and, in some instances, the pasture was described as lush and 2) recommendations suggest that grazing grass-based herbage should meet normal equine vitamin E requirements. Unfortunately, the precise duration of access to pasture required to ensure adequate dietary intake of vitamin E is unknown and probably highly variable, since it is dependent on numerous horse (age, breed, exercise level, unidentified heritable factors) and pasture (herbage type and quantity, season, growth conditions) factors (Blythe *et al.* 1991; Blakley and Bell 1994; DeLaRuaDomenech *et al.* 1997a). For this reason, while it is stated that horses with access to green forage for <3 months/year may have vitamin E plasma concentrations below the normal range (Divers *et al.* 2001), this grazing requirement cannot be extrapolated and used to assess the adequacy of duration of grazing for horses in the present study. Furthermore, most of these grazing horses were also receiving supplementary feeding with concentrates or forage which would have contributed variably to their vitamin E intake.

The low vitamin E status of the grazing group may reflect failure of absorption or retention of dietary vitamin E. In this respect, studies of equine degenerative myeloencephalopathy

suggest there may be a familial predisposition towards low bioavailability of vitamin E (Mayhew *et al.* 1987). Failure to absorb vitamin E may be due to intestinal epithelial absorptive dysfunction or the presence of competing factors within the intestine, such as high levels of dietary polyunsaturated fats (Machlin 1984). Consistent with this possibility, oral vitamin E supplementation of EMND-affected horses produced inconsistent increases in plasma vitamin E (Divers *et al.* 2001) compared with normal horses (Blakley and Bell 1994). Most EMND-affected horses have reduced glucose absorption that reflects abnormalities in intestinal glucose transport (Divers *et al.* 1994, 1997; Benders *et al.* 2001), although a defect at the level of the jejunal luminal membrane glucose transporters is unlikely (Benders *et al.* 2005). Furthermore, those human vitamin E deficiency disorders which lead to neurodegeneration primarily affect patients with gastrointestinal or metabolic disorders that reduce vitamin E bioavailability (Satya-Murti *et al.* 1986). Further investigation of grazing EMND horses using an oral vitamin E absorption test is warranted. Alternatively, the reduced vitamin E levels in grazing EMND cases may reflect excessive utilisation of vitamin E due to exposure to environmental oxidants including iron, cadmium and lead (Dabbagh *et al.* 1994; DeLaRuaDomenech *et al.* 1997a; Hijova *et al.* 2004; Saly *et al.* 2004). Importantly, it is unlikely that the 13 grazing horses developed EMND as a sole consequence of inadequate dietary vitamin E intake, since horses develop EMND only after prolonged (at least 14 months) feeding of a severely vitamin E deficient diet (Divers *et al.* 2002). Alternative causal mechanisms for EMND which are not directly linked to vitamin E (DeLaRuaDomenech *et al.* 1997a) were supported by the observation that, after adjusting for the effects of plasma vitamin E levels, factors including age, turnout type and size, predominant type of concentrate fed and rabies vaccination status contributed significantly to the overall likelihood of EMND (DeLaRuaDomenech *et al.* 1997a,b). These findings suggest that EMND is a multifactorial disorder. Causal factors proposed for human amyotrophic lateral sclerosis include excess iron and copper intake, and occupational exposure to lead, solvents and chemicals (Chancellor *et al.* 1993), but this association remains unproven as other studies failed to show this association (Bergomi *et al.* 2002). Evidence for involvement of trace element toxicosis in EMND includes similarities in the clinicopathological features of EMND and lead toxicosis (Sojka *et al.* 1996), and the presence of elevated levels of copper in spinal cords from EMND cases (Polack *et al.* 2000). Unfortunately, the present study did not reveal any new intrinsic, managemental or environmental risk factors for EMND, possibly in part because of small sample size and the absence of a control group. The retrospective nature of this survey did not allow assessment of the vitamin E content of the pastures the horses had access to, or other physical or forage factors that could influence vitamin E absorption or the absorption of a potential toxic agent. Future work along these lines is planned.

The age of onset, clinical signs and outcome for European EMND cases were broadly similar to those reported previously for North American cases (Cummings *et al.* 1990; Divers *et al.* 1992, 1994).

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