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PATHOLOGY

Hypomagnesemia in beef cattle from the central region of Argentina: retrospective study

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ABSTRACT: *Hypomagnesaemia (grass tetany) is a metabolic disorder of ruminants due to a reduced dietary intake of magnesium (primary deficiency), incorrect digestibility or associated metabolic factors reducing Mg intake (secondary deficiency). Grass tetany is a production disease responsible for important economic losses in beef herds from Argentina. Several factors influence the development of grass tetany in cattle, including physiological status, weather, soil and forage. This research described a retrospective analysis over the past 20 years, revising the cases of beef cattle clinical hypomagnesaemia registered at the Veterinary Diagnostic Service in INTA Balcarce, Argentina.*
Key words: *magnesium, deficiency, cattle, epidemiology.*

Hipomagnesemia em bovinos de corte da região central da Argentina: estudo retrospectivo

RESUMO: *Hipomagnesemia é um distúrbio metabólico de ruminantes devido a uma redução na absorção de magnésio (deficiência primária), digestibilidade incorreta ou fatores metabólicos associados que reduzem a ingestão de Mg (deficiência secundária). Hipomagnesemia é uma doença de produção responsável por importantes perdas econômicas em rebanhos de corte da Argentina. Vários fatores influenciam o desenvolvimento da hipomagnesemia em bovinos, incluindo fatores fisiológicos, clima, solo e forragem. Este trabalho descreve uma análise retrospectiva dos últimos 20 anos, revisando os casos de hipomagnesemia clínica em bovinos de corte registrados no Serviço de Diagnóstico Veterinário do INTA Balcarce, Argentina.*
Palavras-chave: *magnésio, deficiência, bovino, epidemiologia.*

INTRODUCTION

Hypomagnesemia (grass tetany) is a metabolic disorder of ruminants, mainly in adult cattle under grazing conditions, caused by low magnesium (Mg) blood levels. Hypomagnesemia is a complex multifactorial metabolic disease influenced by soil characteristics, diet, weather conditions, and physiological aspects of the cow (LITTLEDIKE et al., 1981; ROBINSON et al., 1989).

Hypomagnesemia is endemic worldwide; especially in extensive farming systems using temperate grasslands and other forage resources (LITTLEDIKE et al., 1981; HARRIS et al., 1983; DUA & CARE, 1995). It represent half of all the metabolic diseases diagnosed by practitioners in beef farms in Buenos Aires province, and the main cause of death in adult cattle in the region (CSEH et al., 1993).

Hypomagnesemia occurrence has been previously associated with certain climatic conditions, during high environmental humidity and low temperatures (GRUNES et al., 1970; ROGERS et al., 1977; HARRIS et al., 1983; ROBINSON et al., 1989; CSEH & CRENOVICH, 1996). Adult cows are commonly affected due to their reduced capacity of dietary Mg absorption (FONTENOT, 1980; LITTLEDIKE et al., 1981; HARRIS et al., 1983; REINHARDT et al., 2011).

Magnesium is absorbed in the reticulum-rumen of ruminants (MARTENS & SCHWEIGEL, 2000). Mg absorption is mainly inhibited by dietary K, among other diet components (LITTLEDIKE et al., 1981). Most Mg (60% to 70%) is found in the bones and poorly available for its physiologic functions in the adult cattle (ROBINSON et al., 1989). Mg metabolism is not regulated by specific hormones

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(MARTENS & SCHWEIGEL, 2000), therefore, its regulation is complex and with poor bioavailability in corporal fluids. Consequently, a constant daily dietary Mg intake is necessary in order to maintain physiological levels, especially during late pregnancy and lactation (LITTLEDIKE et al., 1981). Mg is an essential co-factor of multiple enzymatic reactions and the regulation of the synaptic transmission during excitation - contraction of skeletal muscles. Therefore, Mg deficiency leads to several clinical problems: decrease of voluntary feed intake and ruminal fermentation, neurological disorders and sudden death, when normal magnesemia levels are not achieved (MARTENS & SCHWEIGEL, 2000). Hypomagnesemia is clinical evident when cerebrospinal Mg is below physiological levels, leading to an abnormal nervous system function, more than a dysfunction of the peripheral nervous system (LITTLEDIKE et al., 1981).

The aim of this research was to carried out a retrospective study of clinical hypomagnesemia diagnosed in beef cattle systems of central Argentina, including a 20-year period of the registered information in the Veterinary Diagnostic Service of the National Institute of Agricultural Technology in Balcarce, Argentina.

MATERIALS AND METHODS

Hypomagnesemia outbreaks registered during 20 years (1998-2017) in beef farms of Buenos Aires province, Argentina were retrospectively analyzed. Anamnestic, epidemiological, clinical and biochemical information were used to confirm the etiological diagnosis. Mg blood and vitreous humor levels, as well as Mg, Ca and K levels in forages were tested using atomic absorption spectroscopy (Perkin Elmer AAnalyst 700, CT, USA). Climatic information (temperature and rainfall) was obtained from the meteorological center at INTA Balcarce.

SaTScan™ software (version 9.3) was used to check spatial clusters of 160 outbreaks geolocated in 43 counties of Buenos Aires province. Descriptive statistics were estimated at the different variables registered in each outbreak. Association between mortality in each outbreak and different variables (animal age, breed, body condition and forage grazed) were established using Chi-squared and Fisher's exact test accordingly, using the animal as the study unit.

Association between magnesemia and animal age was evaluated by Kruskal-Wallis test with a significance level 0.05. Proportion of hypomagnesemia outbreaks throughout the period of study was evaluated using a generalized linear model (GLM). Seasonality patterns on hypomagnesemia outbreaks were also tested using a time series analysis (R project) (SHUMWAY, 1988). Space-time permutation scan using each outbreak as the study unit and the centroids of the county was tested by SatScan V.9.3. Spatial visualization of outbreaks was made using choropleth maps (QGis 2.14 software).

RESULTS

Along the 20 years period evaluated in this study, 232 hypomagnesemia outbreaks in beef cattle farms from Buenos Aires province were diagnosed out of 17,967 protocols registered in the Veterinary Diagnostic Service in INTA Balcarce (Table 1). Among these outbreaks, 160 were geolocated in 43 different counties of Buenos Aires province, in order to establish space distribution: 90.5% of hypomagnesemia outbreaks were diagnosed in the south central counties (Figure 1). A geographic cluster of hypomagnesemia outbreaks was detected in Azul, Tapalqué, Rauch and Tandil counties between October 2001 and February 2004, with no statistical significance ($P = 0.072$).

In the 232 outbreaks, 54,103 total cattle were exposed. Of all the exposed cattle, 1,798 died (3.3% mortality rate). Mortality rate ranged from 0 to 28.33% in each affected herd (mean 4.52%). Relative percentage of hypomagnesemia outbreaks versus total of registered cases in the database is shown in figure 2. During 2001, 2010, 2012 and 2013, more hypomagnesemia outbreaks occurred in comparison with the other years of this study ($P < 0.05$). Nevertheless, when comparing proportion of hypomagnesemia outbreaks during these four years, no differences were detected. In order to explain these findings, the meteorological data during this time-period was investigated. No association between annual and monthly rainfall during these 20 years-period and the number of hypomagnesemia outbreaks was detected ($P > 0.05$).

Time series analysis in the period 1998-2017 showed that 78% of the hypomagnesemia outbreaks occurred during winter and spring (June to October), with the peak in August (Figure 3). Autoregressive models were adjusted in order to describe the relationship of number of outbreaks each month, confirming the seasonal pattern (annual and cyclic) ($P < 0.05$).

Multiparous cows were most commonly affected (83.2% of the outbreaks), followed by steers

Table 1 - Clinical hypomagnesemia outbreaks in beef cattle of Buenos Aires province registered during 1998-2017. Total cases (registered at the Veterinary Diagnostic Service database), hypomagnesemia outbreaks (among this database), exposed and deceased animals.

Year	Total cases[1]	-----Hypomagnesemia outbreaks[2]-----		Exposed animals[3]	-------Deceased animals[4]------	
	n	n	%	n	n	%
1998	929	5	0.54	2038	37	1.82
1999	804	11	1.37	3037	100	3.29
2000	969	12	1.24	2195	95	4.33
2001	875	32	3.66	9769	300	3.07
2002	729	4	0.55	760	17	2.24
2003	1070	2	0.19	780	10	1.28
2004	1033	4	0.39	459	22	4.79
2005	1295	9	0.69	712	65	9.13
2006	1100	3	0.27	189	23	12.17
2007	948	6	0.63	1160	20	1.72
2008	899	7	0.78	1150	36	3.13
2009	769	13	1.69	3667	121	3.30
2010	823	25	3.04	9540	343	3.60
2011	976	15	1.54	1526	67	4.39
2012	841	21	2.50	3765	81	2.15
2013	742	18	2.43	2223	57	2.56
2014	739	8	1.08	2919	195	6.68
2015	816	12	1.47	1461	68	4.65
2016	813	10	1.23	3794	56	1.48
2017	797	15	1.88	2959	85	2.87
Total	17967	232	1.29	54103	1798	3.32

[1]Total cases registered in the Veterinary Diagnostic Service database during the year.
[2]Hypomagnesemia outbreaks registered during this year and percentage in comparison with total cases.
[3]Exposed animals in herds where hypomagnesemia outbreaks were registered.
[4]Deceased animals and percentage in comparison with exposed animals in the herd where hypomagnesemia outbreaks were registered.

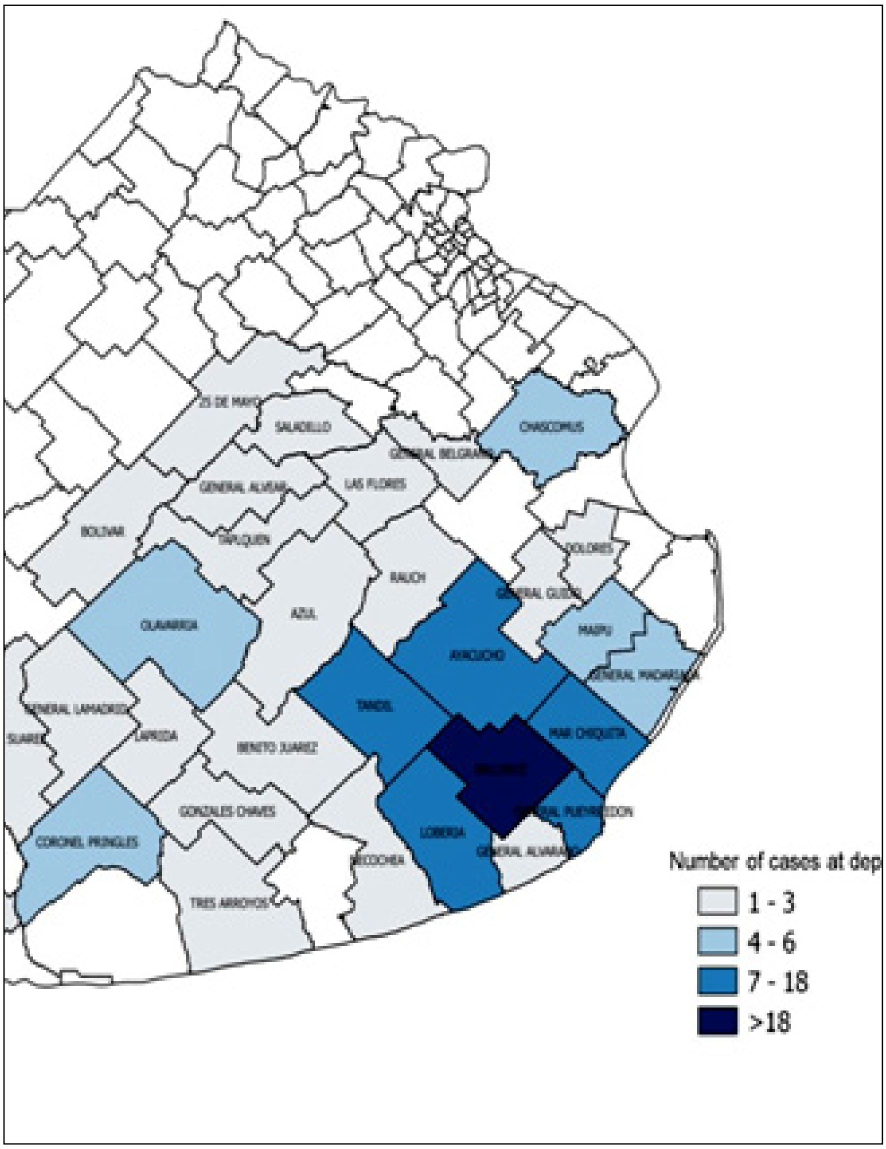
and heifers (10.3%) and calves (2.6%). Animal age was not registered in 3.9% of the outbreaks. Mortality rates were higher in multiparous cows (3.52%) in comparison with the mortality rate in calves (1.67%) and steers/heifers (2.42%): OR 2.15 (CI 95% 1.51-3.06) and 1.47 (1.20-1.79), respectivelly (P < 0.0001).

Scarce data about bovine breed were registered in the hypomagnesemia outbreaks. In 13.9, 3.9, 0.8 and 0.8% of the outbreaks, Angus, Hereford, Charolais or Angus × Hereford cattle were affected, respectively. Mortality rates were higher in Hereford (3.06%) than in Angus cattle (1.85%) (OR 1.67; IC95% 1.26-2.23; P < 0.0005).

According to Veterinary Diagnostic Service reports, 16.8%, 12.9% and 1.3% of the affected cattle had very good, good or regular body condition when the hypomagnesemia outbreaks occurred, respectively. Furthermore, mortality rates in cattle with very good body condition were higher (6.01%) when compared with cattle with good or regular body condition (3.29%) (OR 1.88; IC95% 1.61-2.18; P < 0.0001). Affected cattle were already calved (76.4%), still pregnant (20.8%) or not pregnant (“empty”) (2.8%) when the hypomagnesemia outbreak occurred.

In 33.2%, 20.3% and 7.3% of the hypomagnesemia outbreaks, affected cattle were grazing improved perennial pastures, natural grasslands, or winter annual forages, respectively. In 15.5% of the other hypomagnesemia outbreaks, cattle grazed other forage sources (harvested maize fields or hay, mainly) and in 23.7%, no diet information was available.

Higher mortality rates were recorded in cattle grazing natural grasslands (4.38%) in comparison with cattle grazing improved perennial pastures (3.44%) or winter annual forages (2.56%) (P < 0.0001). According to this analysis, grazing



of natural grasslands were prone to the occurrence of hypomagnesemia outbreaks than cattle foraging improved perennial pastures with (OR 1.29; IC95% 1.15-1.45) or winter annual forages (OR 1.74; IC95% 1.36-2.23). This provided evidence that consumption of natural grasslands by beef cattle in this region may be a risk factor for hypomagnesemia ($P < 0.0001$).

Eighty-three forage samples submitted from paddocks where hypomagnesemia outbreaks occurred were analyzed. In 69.9% of these forage samples, primary Mg deficiency was detected (< 0.20% MS). In 24.1% of the forage samples, high K (>3.00% MS) and low Mg (< 0.20% MS) were simultaneously detected. In 6% of the forage samples, only high K levels were detected. K / (C+Mg) ratio of the different analyzed grasslands are shown in table 2. No association between the occurrence of primary or secondary hypomagnesemia and differential Mg serum levels (see below) in the affected cows were detected in this study (data not shown).

Mg levels in 683 bovine serum samples collected from hypomagnesemia affected herds were analyzed. Mean Mg level was 1.5 mg/100ml (±0.44) (reference level for adult cattle is 1.8-3.2 mg/100ml; Kaneko et al. 2008). No significant difference were detected in the magnesemia in relationship with the age

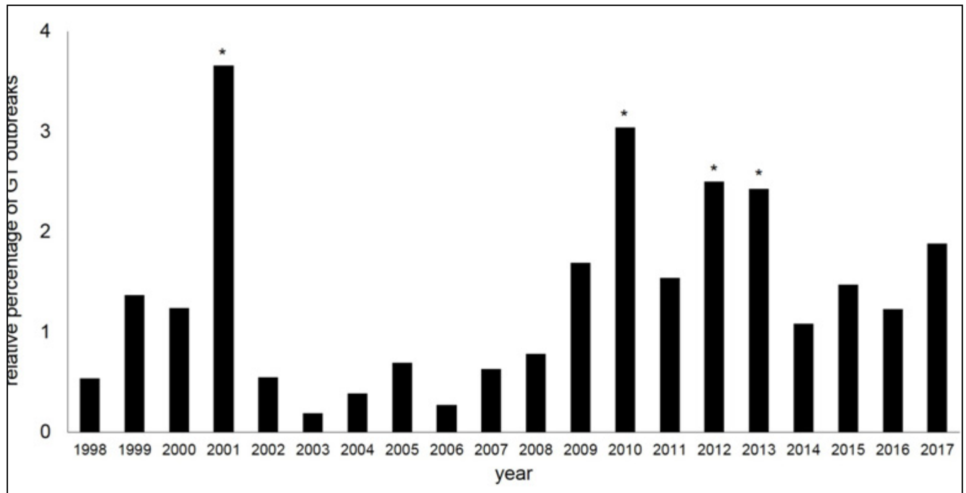


Figure 2 - Relative percentage of hypomagnesemia outbreaks registered in beef cattle in relationship to total cases registered in the Veterinary Diagnostic Service (INTA Balcarce) database during 1998-2017. Outbreaks during years 2001, 2010, 2012 and 2013 were more frequent in comparison with the other years of this study ($P < 0.05$).

of the sampled cattle: calves (1.6 mg/100ml), steers/heifers (1.3 mg/100ml) or adult cows (1.5 mg/100ml) ($P > 0.05$).

Vitreous humor collected during post mortem examination of 125 cattle from hypomagnesemia outbreaks was analyzed. In 71.2% of the vitreous humor samples, Mg levels were below the reference value (> 1.8mg/100ml, KANEKO et al., 2008) with a mean value of 1.57 ± 0.48 mg/100ml.

In most of the hypomagnesemia outbreaks (79.7%) clinical signs compatible were reported:

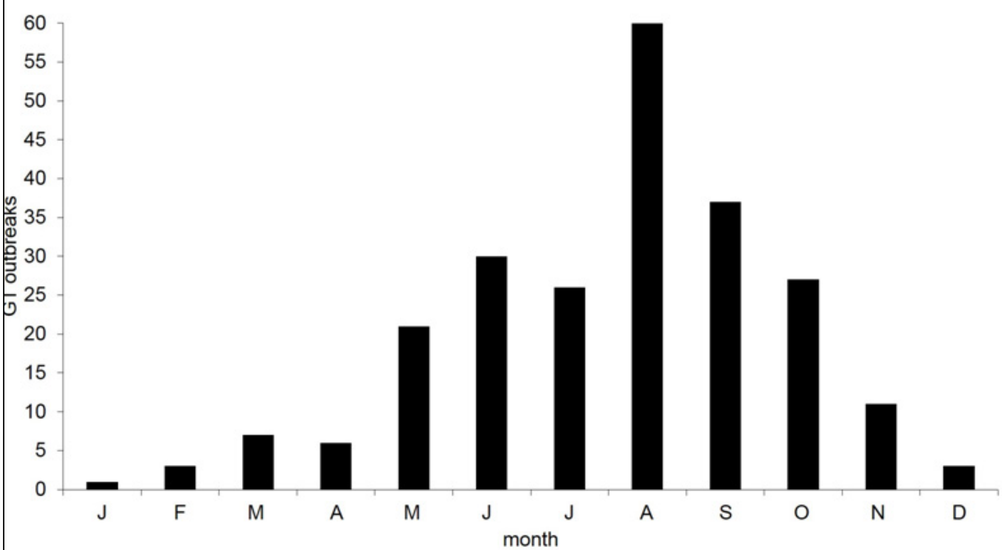


Figure 3 - Month distribution of hypomagnesemia outbreaks registered in beef cattle by the Veterinary Diagnostic Service (INTA Balcarce) during 1998-2017.

excitability, irritability, ataxia, bruxism, ptyalism, recumbence, convulsions, opisthotonus, and tetanic muscular spasms, among other. In the other 20.3% of the outbreaks, no clinical signs were observed before the death of the affected cattle.

DISCUSSION

Hypomagnesemia is one of the most common causes of sudden death in beef adult cattle in grazing systems of the Pampas region of Argentina, according to the historical registries of the Veterinary Diagnostic Service of INTA Balcarce, causing severe economic losses (CSEH et al., 1993). Mortality rates calculated in this study were similar to previous reports in similar production conditions and with high variability (LITTLEDIKE et al., 1981; HARRIS et al., 1983).

Our study confirmed the frequency of hypomagnesemia clinical presentation in central Argentina. Since this was not an organized geographical epidemiology study, it is difficult to confirm if hypomagnesemia is more frequent in counties close to the location of INTA Balcarce. Further studies are necessary in order to confirm the geographical extension of hypomagnesemia problem in grazing cattle from Argentina.

Potential climatic association with hypomagnesemia occurrence has been previously described, showing that environmental humidity and temperature are determinant factors related with alteration in the relationship soil-plant-animal (GRUNES et al., 1970; ROGERS et al., 1977; HARRIS et al., 1983; ROBINSON et al., 1989; CSEH & CRENOVICH, 1996). Furthermore, environmental challenge can also directly affect livestock and this interaction has not been clearly studied (GRUNES & WELCH, 1989). Cattle exposed to low temperature begin to mobilize adipose tissue particularly under low energy diets. Then, lipid mobilization could contribute to hypomagnesemia incidence due to Mg adipocytes uptake or Mg chelation with free fatty acids in the blood (ROBINSON et al., 1989). Our results are in accordance with these previous reports, since most of the hypomagnesemia outbreaks of this report occurred during the winter season and when beef cattle is probably in negative energy balance. Furthermore, hypomagnesemia occurrence is also influenced by body condition (HARRIS et al., 1983), associated with an increased postpartum lipolysis for energy supply (MARTENS & RAYSSIGUIER, 1979). Conversely, other authors suggested that hypomagnesemia is also frequent in low body condition cattle due to the energetic deficiency and susceptibility to chronic hypomagnesaemia in association with climatic distress (MARTENS & RAYSSIGUIER, 1979; MARTENS & SCHWEIGEL, 2000). Avoiding excessive body condition is a key factor in order to control important losses due to hypomagnesemia during the critic season in beef cattle (HARRIS et al., 1983). The positive association between hypomagnesemia occurrence and the physiological status of the affected cows (pregnancy or calved) is probably related to the negative energy balance during the last stages of gestation and first weeks of lactation, even when the cows are receiving Mg supplement, and associated with an inadequate Mg intake or interference of Mg absorption in the digestive tract (ROGERS et al., 1977; DUA & CARE, 1995).

Late pregnancy and lactation are commonly associated with occurrence of hypomagnesemia in cattle due to the high Mg flow to the fetus and the mammary gland (FONTENOT, 1980; ROBINSON et al., 1989). This study showed similar findings, since the seasonal hypomagnesemia presentation is related to the calving season in the central region of Argentina.

In our study, hypomagnesemia was more commonly diagnosed in adult cows and this

Table 2 - Calcium (Ca), Magnesium (Mg) and Potassium (K) concentration, tetany-potential (K/Ca+Mg) in different fodders sampled and analyzed during hypomagnesemia outbreaks.

Forages	Ca%	Mg%	K%	K/Ca+Mg
Natural grasslands	0.28	0.15	1.51	1.45
Improved pastures	0.25	0.12	1.67	1.97
Winter annual grasslands	0.26	0.11	3.34	4.21
Reference values*	≥0.40%	≥0.20%	≤3.00%	≤2.2

*reference values (ALLCROFT & BURNS 1968; GRUNES et al., 1970; JOLLEY & LEAVER 1974; GRUNES & MAYLAND 1984; GRUNES & WELCH 1989).

information could be related with the reduced capacity of dietary Mg absorption (FONTENOT, 1980; LITTLEDIKE et al., 1981; HARRIS et al., 1983; REINHARDT et al., 2011).

More studies are needed in order to confirm the association of different breeds as a risk factor for hypomagnesemia. HARRIS et al. (1983) showed differential morbidity rates in Angus (2.20%) and Hereford (1.19%) cattle.

Hypomagnesemia occurrence is closely related with the composition of the diet. Forage recommended Mg levels is higher than 0.20% DM (>2.0 g/kg) in pregnant or lactating cows (ALLCROFT & BURNS, 1968; GRUNES et al., 1970). Diets with high N (40g/kg DM) or K (30g/kg DM) levels are considered dangerous; therefore, Mg concentration should be higher than 0.25% DM (JOLLEY & LEAVER, 1974; GRUNES & WELCH, 1989). In accordance with these previous reports, low Mg levels and/or excess of K levels were detected in most of the forage samples collected from the paddocks were hypomagnesemia was detected.

Cattle grazing regrowth grasses are usually predisposed to hypomagnesemia. Rapid regrowth of pastures after a cold and wet season generated an increase in the N and K concentration and reduced hydrosoluble carbohydrates, predisposing to hypomagnesemia (MARTENS & RAYSSIGUIER; 1979, ROBINSON et al., 1989). Forage K / (Ca+Mg) ratio has been used for the prediction of hypomagnesemia in grazing cattle. Forages with K / (Ca+Mg) ratio greater than 2.2 could predispose to hypomagnesemia (ALLCROFT & BURNS, 1968, GRUNES et al., 1970). Also, nitrogenous fertilization could increase hypomagnesemia occurrence (GRUNES & WELCH, 1989). Previous studies in the region described 0.18 to 0.21% of Mg in the forage of the same geographical location of this study. However, more variable K concentrations were observed, between 1.72 to 3.94%, describing both forages prone to primary or secondary hypomagnesaemia (CSEH & CRENOVICH, 1996). Besides K, Ca and Mg forage concentration for the prediction of hypomagnesemia, high protein content of the grasslands could diminish Mg bioavailability (HEAD & ROOK, 1957, GRUNES & WELCH, 1989). We only analyzed Mg, K and Ca concentration in the sampled forages of these hypomagnesemia outbreaks. Low Mg and high K levels were simultaneously or individually detected in these samples. Further studies are needed in order to better characterize the quality of these diets and their association with the occurrence of hypomagnesemia in cattle from this region.

Magnesium serum level is the best indicator of Mg status in the animal and Mg intake (HERDT et al., 2000). Similarly, mean Mg serum levels were low in samples collected from hypomagnesemia affected herds. However, low serum Mg levels are not necessarily useful for hypomagnesemia prediction and cerebrospinal fluid Mg levels are better correlated with neurological signs (MARTENS & SCHWEIGEL, 2000). Post mortem diagnosis of hypomagnesemia is difficult and evaluation of Mg in vitreous humor is useful in this condition (MCCOY, 2004), in accordance with our results were more than 71% of the humor vitreous samples analyzed from cattle of affected herds had low Mg levels. Previous studies have shown that levels of Mg in vitreous humor between 1.56 and 1.32 mg/100ml are good indicators of hypomagnesaemia and hypomagnesemia in adult cattle, when the sample is collected 24 or 48 post mortem, respectively (MCCOY, 2004).

Hypocalcaemia is frequently detected in cattle with low blood Mg levels (ALLCROFT & BURNS, 1968). Interference of Ca homeostasis in cattle with hypomagnesaemia could precipitate tetany (JOLLEY & LEAVER, 1974; VAN MOSEL et al., 1991; REINHARDT et al., 2011). However, Ca levels were not evaluated in the hypomagnesemia cattle during this study in order to corroborate this finding.

Clinical signs reported in the outbreaks of hypomagnesemia included in this research were similar to the previously described (ROGERS, 1979; MARTENS & SCHWEIGEL, 2000). Subclinical cases were described; cattle may demonstrate anorexia, low milk yield, anemia, mild nervousness, long labor lasting and edema of the mammary gland (ROGERS, 1979). Nevertheless, under extensive production systems, sudden death with no previous observation of clinical signs is common.

Pathological findings on the hypomagnesemia affected cattle were not evaluated in this study. Nonspecific lesions have been described in cattle, like multifocal serosal hemorrhages in different tissues (LITTLEDIKE et al., 1981).

Management practices in order to prevent hypomagnesemia presentation will depend on the urgency or severity in any farm. Once clinical signs are observed, endovenous administration of Mg and Ca solutions are necessary in order to prevent the death of the affected cattle. Correct treatment of cattle once the first hypomagnesemia signs are observed, and usually effective. However, 30% of the affected cattle may die after treatment (LITTLEDIKE et al., 1981; HARRIS et al., 1983). Movement of the affected herd to a different paddock, or the oral Mg and energy supplementation is useful once the first hypomagnesemia signs are observed. Before the critical hypomagnesemia season, other management practices recommended, mainly providing forages with more than 2g of Mg / kg DM or the inclusion of daily Mg oral supplements (ROBINSON et al., 1989; ODETTE, 2005). The inclusion of Mg oral supplements is frequent in affected farms of the region, but unfortunately, with ambiguous success. Hay inclusion in the diet is also recommended, especially with the inclusion of legumes as their mineral concentration could reduce the occurrence of more cases (HARRIS et al., 1983; ROBINSON et al., 1989).

Differential diagnosis of hypomagnesemia should be carried after the occurrence of rapid onset of death in adult beef cattle during the winter season in Central Argentina as anthrax and bacillary hemoglobinuria, since they are also endemic in the region (SPÄTH & BECKER, 2012). We differentiated these diagnoses based on epidemiological, clinical, pathological findings and complementary analyzes.

CONCLUSION

Hypomagnesemia in beef cattle of the central region of Argentina cause 3.3% of mortality of the affected herds, occurring mainly in adult cattle during the winter and early spring seasons, consuming natural grasslands.

DECLARATION OF CONFLICT OF INTEREST

None of the authors has any other financial or personal relationships that could inappropriately influence or bias the content of the paper.

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AUTHORS' CONTRIBUTIONS

GJC conceived and designed experiments. GJC, ELF, JIP and ERO performed the experiments. ELF and JIP carried out the lab analyses. GJC and ERO supervised and coordinated the animal experiments and provided clinical data. EJAS, GM and FCM performed statistical analyses of experimental data. GJC and FCM prepared the draft of the manuscript. All authors critically revised the manuscript and approved of the final version.

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