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Polioencephalomalacia in ruminants caused by excessive amount of sulphur - a review

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Abstract

Polioencephalomalacia as a result of sulphur excess is a growing problem in cattle and sheep, mainly in young, growing animals. It is common in different regions of the world. The disease develops favoured by certain conditions such as sustained provision of feed and water with high sulphur content, use of dietary supplements containing sulphur, and a habitat with high hydrogen sulphide concentration. Pathogenesis of the disease is complex, but very important are oxidative-antioxidative imbalance, dysfunction of vessels, and secondary cerebral cortex ischaemia as a result of direct and/or indirect action of sulphur metabolites, namely hydrogen sulphide, sulphides, and sulphites. Clinical signs and changes in the cerebral cortex in the form of degenerative necrotic lesions are similar to those observed in polioencephalomalacia caused by vitamin B_1 deficiency, and lead and salt intoxication. Highly increased sulphur content (more than 0.3-0.4 of dry matter) in the diet is the basis for differential diagnosis, as well the high concentration of hydrogen sulphide in gas and sulphides in rumen fluid. In prophylaxis and treatment the most important measure is to limit sulphur intake and in acute cases to neutralise low pH in rumen and administer vitamin B_1 injections.

Key words: cattle, sheep, polioencephalomalacia, sulphur.

Introduction

Polioencephalomalacia (PEM, cerebral cortex necrosis) in cattle can develop from different determinants, but most often as a result of vitamin B_1 deficiency and heavy metal intoxication. Recently it has also been diagnosed after sustained feeding with concentrates or the use of supplements with high sulphur content. While pathogenesis of PEM due to vitamin B_1 deficiency and intoxication is relatively well known, the PEMES (polioencephalomalacia from excess sulphur) as a result of moderate but sustained excess of sulphur is still a matter of discussion and controversy. Results of clinical observations and experimental research are often divergent and mainly concern its possible role in the aetiology of the deficiency and metabolic disturbances of vitamin B_1, which also contains sulphur in its chemical structure. In animals with PEMES, different concentrations of vitamin B_1 in plasma were found, from deficiency to very high levels. The reactions of animals to vitamin B_1 administration differ. The great similarity of clinical symptoms and changes in the cerebral cortex provided the impulse for studies on connections between PEMES and PEM.

The pathogenesis of PEMES and methods of its diagnosis may still be an open matter, however it is important from the cognitive and practical point of view. The number of diagnosed cases is rather small, but it does not reflect the real prevalence of the disease. It is difficult to eliminate its false identification as PEM from a different determinant due to the strong similarity of signs and lesions and the low availability of differentiating diagnostic methods. PEMES will become a growing problem in the future, considering the increasingly frequent use of supplements with sulphur in intensive crop farming and animal feed, and the significant current SO_2 emission to the atmosphere.

Aetiology and occurrence

The large content of sulphur in the diet and limited ability of the organism to use and neutralise its excess is the cause of PEMES. The kind of sulphur compound

should not be aetiologically neglected, as well as the feed ration structure, age, or individual predisposition of the animal. Therefore, from literature data, the disease could probably already occur at 0.4% content of sulphur in dietary dry matter, while in a different case no clinical signs were observed at 0.81% content in dietary dry matter (19, 21, 29). Absorption of sulphur is relatively high in ruminants and derives from non-organic compounds, mainly from sulphates, much less from organic compounds, and in small measure from elementary sulphur. Most often young cattle become ill during the grazing period, and the first cases of the disease occur between the 15^{th} and 45^{th} days of grazing (14, 23). Usually only a small number of animals show clinical signs, but the characteristic changes of high concentration of hydrogen sulphide (H_2S) and sulphides in rumen fluid and degenerative necrotic lesions in the cerebral cortex have also been found in apparently healthy animals (23, 29). The cause of the disease can be a single component diet fed over a sustained period and containing ingredients with high sulphur content, especially by-products from the mining and food industries. Mining and industrial water, cruciferous plants, some concentrates and milk substitutes, and also molasses and spent grain have high sulphur content (5, 13, 17, 20, 21, 24, 29). The ingestion of sulphur with water can be exceptionally high in situations of drought and high temperature when animals drink heavily (14, 23, 34). It was shown that cows at ambient temperature of 21°C consumed about 64 l of water daily, which is about 77 g of sulphur and exceeds the daily requirement in the whole feed ration (14), 2100 ppms sulphates in water, which is equivalent to 700 ppms of sulphur, results in an increase in sulphur concentration in the whole diet to over 0.5% of dry matter (9).

Water with a high concentration of sulphates easily induces PEMES symptoms both in natural and experimental conditions (2, 12, 14). Similarly, an acute course of the disease leading to deaths was observed in single-component feeding with cruciferous plants (24), in which sulphur content is 3-5 times higher than in other plants commonly used in cattle feeding. In cruciferous plants it is about 1.5 % of dry matter, but only slightly lower concentrations can be found in fodder plants from industrial areas. PEMES was observed also in cattle kept in barns with a high H_2S concentration in the air (9). High content of this gas is found in barns with residual slurry, which are inadequately ventilated. A concentration of H_2S in the air higher than 150 ppm causes mucosal layer irritation, respiratory disturbances, and can induce PEMES (5). As H_2S is heavier than air, it has a tendency to stay in barns, especially those with windows and ventilators placed high (5).

A large amount of carbohydrates, deficiency in raw fibre, the presence of sulphur antagonists (mainly copper (4)), and perhaps also disorders in the synthesis and metabolism of vitamin B_1 (5, 31), promote the development of the disease. The cause of acute sulphur intoxication and PEMES can be excessive administration of various sulphur compounds for the purposes of prevention, treatment, and improving production results (18, 33). The suspicion may also fall on sulphur amino acids, which are not essential for proper functioning of the organism, but which in the case of their excess, produce large amounts of sulphates (1, 38).

There is a gradual increase in PEMES cases with quite acute clinical signs in different regions of the world (24, 31). The disease has been observed even when the excess of sulphur in the diet was small and it can affect a large number of animals (19, 24, 31). It is probably the result of a decreased tolerance for sulphur excess in animals with increasingly higher productivity and a highly stimulated metabolism. Sulphur content in industrial gases and the atmosphere as the cause of the disease should not be neglected.

Pathogenesis

Initially PEMES was associated with deficiency in and metabolism disorders of vitamin B_1. The clinical manifestations and histopathological lesions in the brain which characterise both are very similar and additionally some experimental results confirmed the existence of unspecified connections between both disorders (21, 24). Goonerathe *et al.* (8), feeding 6-week-old lambs food high in sulphur (0.63% of dry matter) induced PEMES in 2-3 weeks of experiment, but when they additionally administered vitamin B_1 (230 mg/kg of dry matter) clinical symptoms of the disease were not observed. A vitamin B_1 supplement prevented clinical signs, but surprisingly, the concentration of vitamin B_1 in lambs with PEMES not receiving vitamin B_1 was high, which, according to the authors' suggestion, could be a result of its increased release from tissues. In post mortem examination, necrotic lesions in the cerebral cortex were found in all lambs, but were denser in the group not receiving vitamin B_1. In lambs given feed supplemented with sulphur and vitamin B_1, the clinical signs were not seen, but microscopic lesions were observed in the brain, however, no changes in B_1 concentrations in plasma and tissues were noted (32). Neville *et al.* (28), imposing a diet high in sulphur (0.73%–0.87% of dry matter) and simultaneously vitamin B_{12} supplements (50, 100, and 150 mg/animal/d) did not observe the disease, but the concentration of H_2S in the rumen increased to 1.07g/m^3. However, the results of most studies both experimental and field do not confirm the direct influence of vitamin B_1 deficiency or supplement on PEMES development or on the course of the disease's clinical symptoms. In animals with PEMES, the normal concentration of the vitamin B_1 was estimated (12, 19, 20, 23), and its injection or diet supplementation did not influence the development or

course of the disease (18, 19). Among others, Kul *et al.* (19), analysing the massive outbreaks of PEMES in dairy cows and feedlot cattle with typical lesions caused by monotonous feeding barley malt with increased sulphur content (0.45% of dry matter), did not observe a positive reaction to vitamin B_1 injection. Similarly, Jeffrey *et al.* (18) did not state the downward influence of vitamin B_1 supplement on the cases of illness in lambs and calves not showing an initial deficiency of this vitamin. It does not exclude a non-specific protective effect of vitamin B_1 on brain tissue. Clinical symptoms appear with the existence of degenerative necrotic lesions, which are usually irreversible, and this fact to some degree can explain the ineffectiveness of treatment with vitamin B_1.

Most of the studies show that the most important element in the pathogenesis of the disease is direct or indirect action of H_2S, sulphides, and sulphites on the cerebral cortex. A high correlation was found between the H_2S concentration in the rumen gas and sulphides in the rumen fluid and the development of characteristic clinical symptoms and lesions in the brain (4, 11, 12, 20). In PEMES induced experimentally by adding sulphates to feeds for young cattle, H_2S concentration in the gas was 17-60 times higher and sulphides in the fluid about 4-7 times higher than those in control animals (11, 19, 20). Such high concentration of H_2S in the rumen gas can result from the increased reduction of sulphur and its compounds ingested in feeds and water. On the other hand, it can be the result of the limited possibility for uptake of the excess sulphur for the synthesis of amino acids and proteins and possibly the result also of a lower ability to metabolise, neutralise, and eliminate it.

The speed of reduction of sulphur largely depends on the activity of different anaerobic bacteria which exist in the rumen. Various factors probably influence the reductive activity of the bacteria; among them the amount and kind of sulphur compound in the diet, diet composition, and the pH of rumen contents (4, 28). The reduction process is not fully understood yet. Studies are incomplete and concern only selected sulphur compounds, bacterial strains, and animals of strictly defined age (3). Quite interesting are the results of experimental studies on lambs, which were fed a diet with added sodium sulphate (4). Increased H_2S content in the rumen was observed only on the 12^{th} d of the experiment and it was associated with development of clinical signs of PEMES. The lower ability to produce H_2S in the initial period suggests the need for bacteria to adapt in the case of moderate sulphur administration before they generate toxic amounts of H_2S. To some degree it explains why PEMES signs appear only after a long period from the moment of introduction of a sulphur supplement to the diet. It is striking why the introduction of an excess amount of sulphur to the diet can cause development of toxic signs even on the first days, whereas PEMES lesions only develop after two to three weeks. It depends largely on the level of sulphur excess and H_2S concentration in the rumen, but why the lesion formation process does not develop simultaneously with the detectability of toxic signs still remains the question. In cattle, which received 0.1-0.2 g/kg b.w. of sulphur, diarrhoea and decreased appetite during the first 3 d, and lethargy and decreased appetite in the 3^{rd}-4^{st} week of the experiment were observed (25).

Theoretically, a more complex course and mechanism of symptom development can be considered. Initially the reduction process of sulphur to H_2S predominates. H_2S in large concentrations causes dysfunction of the nervous and respiratory systems with the possibility of death. But quite fast acidosis of rumen develops, which inhibits proliferation and activity of microorganisms including reduction by bacteria. The concentration of H_2S decreases and thus symptoms are limited or inexistent. With time there occurs a relative adaptation of the organism and reduction of bacteria to the excessive sulphur, followed by a moderate re-increase of H_2S concentration with the possibility of PEMES development. To some degree it is confirmed by one of the first observations possibly pointing to PEM due to excess of sulphur (39). As a result of intoxication of young cattle with a concentrated mixture high in sulphur, most of the animals died suddenly, but some of them survived and after 7-10 d they developed characteristic PEM symptoms. Normally H_2S is quickly utilised for synthesis of amino acids and sulphides. Absorbed sulphides are also quickly oxygenated to sulphates in the liver and they are in turn passed to extracellular fluids and eliminated with urine or return to the intestines or the rumen with saliva.

Beside H_2S, a large concentration of soluble sulphides in the rumen is also pathogenic. Sulphides given to lambs in large amounts *via* the oesophagus cause clinical signs of nervous system dysfunction in the form of lethargy, spasms, and poor vision after a short period of time as 20 h (22). Some role can be played by deficiency in Cu, Mo, Zn, and Ca, which bind sulphur producing poorly soluble sulphides (5).

The mechanism of the detrimental effect of H_2S on the cerebral cortex and organs is still not explained. It seems that depending on concentration and conditions, it can act protectively or toxically (37). In physiological concentrations, similarly to nitrogen and carbon oxides H_2S, plays the role of gas transmitter and neuromodulator. It can coact anti-oxidatively, anti-inflammatorily, and anti-apoptotically. In neurodegenerative diseases in people, like Parkinson's and Alzheimer's disease, disorders in the production and metabolism of H_2S have been found. The presence of H_2S makes possible of using it in prevention and treatment of this kind of diseases (16). In large concentrations, H_2S increases oxidative processes and thus the generated free sulphite radicals can damage cerebral neurons (32).

Sulphites are produced in cattle in the rumen, mostly during amino acid catabolism, and in organs in the process of sulphite oxidation, but also when cattle are in an environment with high sulphur dioxide concentration.

Mice after SO_2 inhalation indicated an increased sulphite concentration and presented ultrastructural damage in organs including cerebral cortex neurons, and increased numbers of apoptotic splenocytes (26, 27). It is worth noting that sulphites are used as a preservative in the production of silages. Sulphites show high biochemical activity and are neutralised by sulphite oxidases (5).

Decreased activity of sulphite oxidases, as a result of molybdenum deficiency and tungsten and sulphite addition, reduces the organism's antioxidative ability and total oxidative status (TAS) and increases lipid peroxidation (15, 36). Antioxidative ability can be decreased also by other sulphur metabolites and its compounds, *e.g.* homocystein produced in the process of methionine metabolism to H_2S. Probably the correct homocystein to H_2S ratio is necessary. By analysis of results of different studies, it can be concluded that the pathogenesis of PEMES is complex. Symptoms and degenerative necrotic lesions in the brain are probably the result of direct and/or indirect influence of different compounds and sulphur metabolites, namely H_2S, sulphides, and sulphates, which cause oxidative-antioxidative imbalance, vessel dysfunction, and cerebral cortex hypoxia. In the mechanism of PEMES development, one should also consider the imbalance between the speed of sulphur compound reduction in the rumen and the degree of utilisation and neutralisation of metabolites for synthesis of sulphur amino acids and metabolic neutral compounds.

Clinical symptoms and anatomo-pathological changes

Clinical symptoms and necropsy including case history may suspect PEMES but unfortunately cannot provide its confirmation, which can be done by accurate laboratory tests. General clinical symptoms and the course of the disease differ depending on the source and the amount of excess of sulphur, feed ratio composition, environmental conditions, age, and individual sensitivity of the animals. Most frequently morbidity blights single animals and is not simultaneous across the herd. It can occur suddenly or gradually increase. Young animals at different age are affected first, sometimes with rather acute symptoms causing deaths. In subclinical form and at the initial phase of the disease only lower appetite and lower weight gain or milk production are observed and a large increase in H_2S concentration in rumen gas is the specific change (10, 40). In the advanced clinical form, different neurological signs dominate depending on the phase of the disease: lethargy, muscle contractions, hypersensitivity, ataxia and lack of coordination, head pressing on walls, contractions of whole muscle parts (lockjaw, stiff neck), and central cortical blindness. Finally, the animals die with symptoms of complete blindness and paralysis that can be preceded or accompanied by disorders of the digestive and respiratory systems.

The necropsy of the animal died of PEMES has no defining peculiarity with the exception of the characteristic smell of hydrogen sulphide from rumen contents (if the necropsy is performed shortly after death) and the presence of degenerative necrotic foci in the brain. Quite often hyperaemia and inflammation of mucosal membranes, a light yellow liver, and dark coloured kidneys are observed (5). Morphological and histological changes in the brain are relatively distinctive. They occur very early, before clinical symptoms appear. They are noted in animals seemingly healthy and without specific subclinical symptoms in herds with a few clinical cases of the disease (8) and in experimental animals before symptoms appear (29). Typical changes are as follows: diffused degenerative necrotic foci undergoing malacia or liquefaction, and changes with spongious structure in the cerebral cortex, but also in the interbrain and brain stem (14). Degeneration and necrosis of neuron cells, leucocyte infiltrations around small blood vessels, and hypertrophy of gliomatous tissue dominate in the foci with spongious structure. Excavasations, capillary vessels hypertrophy, and fibrous degeneration of arterioles are also observed. (19).

Differential diagnosis

Diagnosis of PEMES based only on physical examination and histological changes in the brain is always doubtful as similar symptoms and lesions can also have different determinants (35). In differential diagnosis, first of all, PEM caused by deficiency in and metabolism disorder of vitamin B_1 and several intoxications, mostly with lead, molybdenum, and sodium chloride should be considered. PEM can be caused by vitamin B_1 deficiency or the presence or excess of the aforementioned toxins in blood and tissues.

Diagnosis of PEMES is complex and should be based on: medical history regarding diet ratio and possible usage of sulphur preparations; clinical signs and course of the disease; sulphates or sulphur determination in the feed and water; H_2S determination in rumen gas and fluid; post mortem examination of the brain. Helpful are also: observation of a brain section in ultraviolet light; thiosulphate determination in urine; determination of methaemoglobin and sulphaemoglobin in the whole blood, and transketolase activity in red blood cells. The transketolase activity does not change, contrary to PEM or B_1 deficiency where it increases greatly (5).

In the case of doubtful results, it is worth determining vitamin B and lead concentrations in blood and tissues. The basic diagnostic method is H_2S determination in gas and sulphites in rumen fluid. Methods of sampling and determination of H_2S are not too complicated. According to Gould *et al*. (11) it is advised to collect gas in a syringe by rumen wall centesis and then to determine H_2S using modified commonly used detectors.

Less accurate is gas collection by nose-rumen catheter and direct determination by a detector. It is possible to determine H_2S gas excreted during rebounding or in environmental air and air exhaled from the lungs. Since concentration of H_2S in rumen gas increases many times before clinical signs occur, this method can be used to determine the risk of disease occurrence and to diagnose subclinical forms. PEMES was observed in the case of sulphate excess in drinking water (2200 ppm), in which there was no large increase in H_2S in rumen gas, but it pertained to animals with advanced symptoms, very limited thirst and appetite and a sudden fall of sulphur ingestion through their diet (3). Sulphate determination in the rumen fluid is less helpful due to smaller differences in concentration between healthy and sick animals. Autofluorescence is clear and convincing in the initial phase of the disease where degenerative changes dominate (9). Unfortunately, it is not specific because it also occurs in PEM with vitamin B_1 deficiency and in lead intoxication. Thiosulphate concentration in the urine, similarly to H_2S in rumen gas, increases greatly before clinical signs occur (6).

Prophylaxis and treatment

Prophylaxis and treatment of PEMES are relatively easy. It is enough to adjust sulphur intake to requirements by eliminating nutrients and preparations high in sulphur from the diet (14, 19). Usually it inhibits the disease's development in less advanced cases, the symptoms disappear and there are no new cases. Spontaneous regression of symptoms can happen despite continuation of a diet high in sulphur (8). The optimal dosage of sulphur to ensure proper metabolism should be around 0.18%-0.20% of dry matter in the feed.

It is recommended to administer vitamin B_1, which improves metabolism in the brain and therefore protects animals from the development of degenerative necrotic lesions and facilitates their healing (24). In acute cases, it is recommended to administer orally alkalising preparations, such as sodium bicarbonate, calcium carbonate, or magnesium oxide, to increase pH and remove acidosis (5). Neutralisation of acid components of the diet with a 2% solution of sodium hydroxide is advised.

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