DIAGNOSTIC EXERCISE

From The Davis-Thompson Foundation*

Case #:**235**; Month: **April**; Year: **2024**

Answer Sheet

Title: Mycotoxic leukoencephalomalacia in a mule

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Clinical History: An outbreak of neurologic disease in mules occurred in Pará, northern Brazil, and affected 13 out of 80 mules. Until one week before the outbreak, the 80 mules were supplemented daily with 60 kg of ground whole corn (a mixture of corn ground together with the straw and corncob) and 30 kg of African palm oil meal. One week before the outbreak, food was increased to 150 kg of ground whole corn, 60 kg of African palm oil meal, and 120 kg of poultry litter. One mule was evaluated because of compulsive walking, blindness, and head pressing (Fig. 1). The patient died 12 hours from the onset of clinical signs.

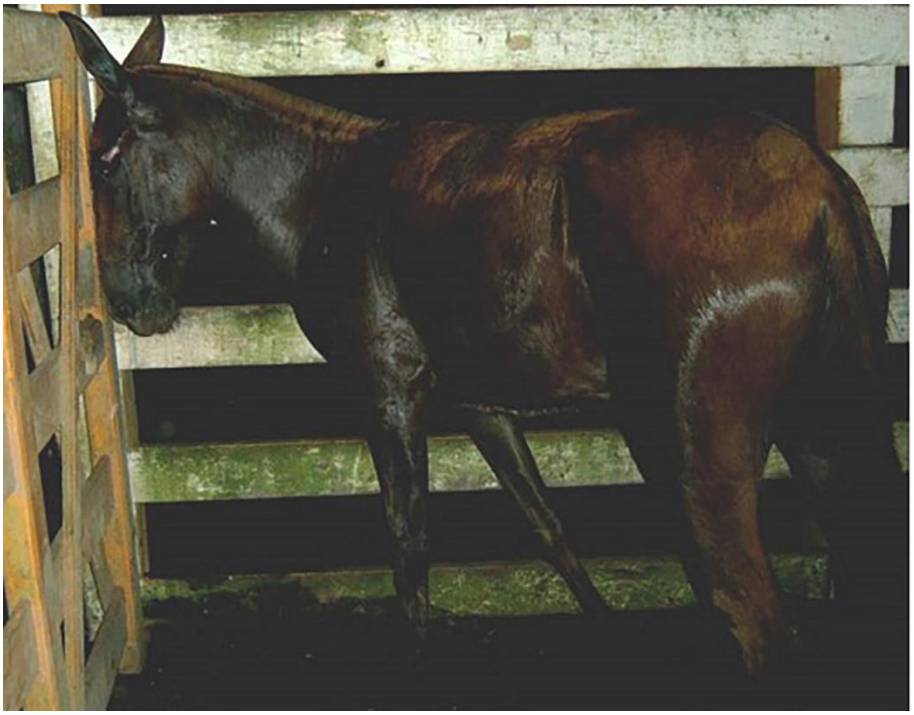

Figure 1. Affected mule with head pressing.

Necropsy findings. The left cerebral hemisphere was enlarged with flattened gyri. The cut surface of the left hemisphere and the cerebral white matter (centrum semioval and corona radiata) had red areas of hemorrhage and necrosis or yellow areas of edema. Similar regions occurred in other areas of the brain, mainly the thalamus and mesencephalon. The liver was swollen and yellow.

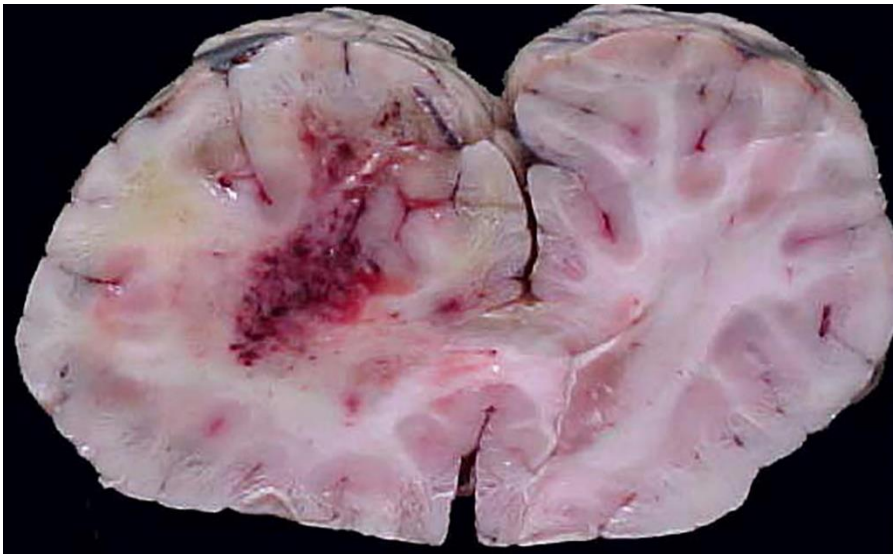

Figure 2. Spontaneous poisoning by fumonisin in a mule. Cross section of the brain reveals asymmetry due to enlargement of the left hemisphere. The white matter has an extensive red and soft area (hemorrhagic necrosis) surrounded by yellow, edematous white matter.

Microscopic Description: There was necrosis of the white matter characterized by disruption and vacuolation of the parenchyma with hemorrhage and edema and swollen of vascular endothelium; perivascular eosinophilic globules were occasionally seen. Swollen astrocytes with eosinophilic cytoplasm and dark marginated nuclei (clasmadendrocytes) were also observed. Cavitations were sometimes observed in the center of the lesion.

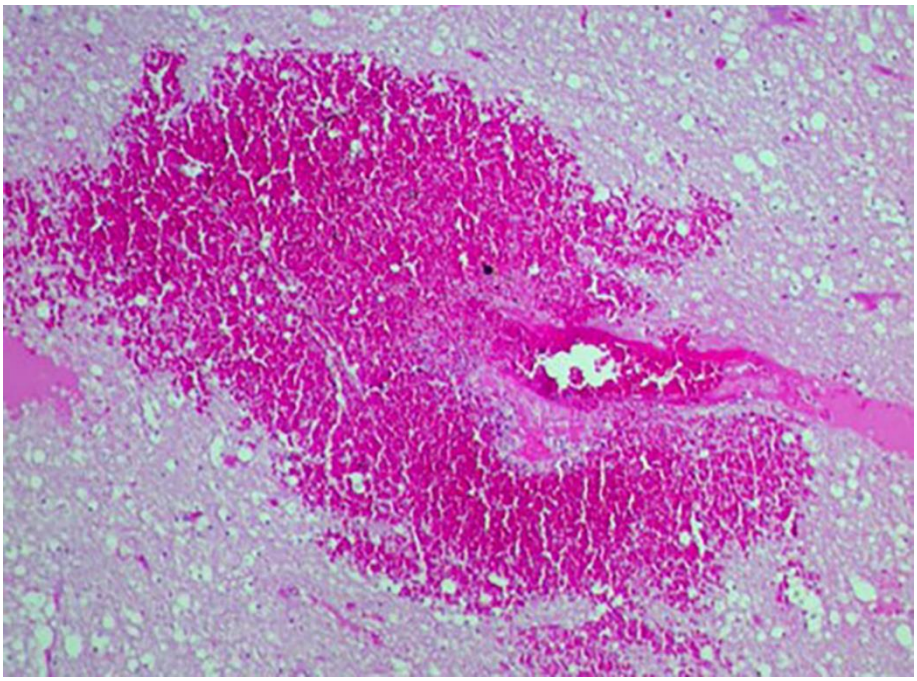

Figure 3. Spontaneous poisoning by fumonisin in a mule. Cerebrum, subcortical white matter. Severe hemorrhages and vacuolization of the white matter.

• **Morphologic diagnosis**: Cerebrum, hemorrhagic white matter necrosis and edema, acute, severe
• **Cause:** Poisoning by fumonisin
• **Name of the condition**: Mycotoxic leukoencephalomalacia

Comments: Mycotoxic leukoencephalomalacia (MLEM) is a disease of Equidae (donkeys, mules, and horses) caused by fumonisins produced by fungi of the genus *Fusarium*, mainly *F. verticillioides* and less frequently *F. proliferatum* (syn. *F. moniliforme*) and *F. subglutinans*, which contaminate corn grains or their by-products. There are 28 types of fumonisins; the most frequent are fumonisins B1, B2, and B3, with B1 being the most toxic. Fumonisins act by altering the myelin because they have structural similarities to sphingosine, the precursor of the sphingolipids that constitute myelin. They work by inhibiting ceramide synthase, an essential enzyme in sphingolipid biosynthesis*. F. verticillioides* and *F. proliferatum* proliferate in corn before or immediately after harvest and at different temperatures, so the disease occurs in different regions worldwide. In Brazil, MLEM was diagnosed for the first time in the state of Rio de Janeiro (7). Later, it was diagnosed in Rio de Janeiro, Rio Grande do Sul, Paraná, Santa Catarina, São Paulo, Minas Gerais, Mato Grosso do Sul, Mato Grosso, Goiás, Paraíba, Pernambuco, and Pará (1,2,6,8,9). These data suggest that MLEM is present in all Brazilian states. MLEM has also been reported in Uruguay (10) and Argentina (3,5).

The intoxication occurs by ingesting whole green or mature corn, corn bran, other by-products from human food processing, and ground whole corn (a mixture of corn, corn stalks, and corncobs (4,8,9). Generally, the poisoning occurs when feeding more than 1 kg of corn daily or with rations containing more than 20% of corn (8,9). In southern Brazil, the mean moisture in 21

samples of corn associated with MLEM outbreaks was 16.98±2.30%, varying from 13.4% to 21%. Five samples had less than 15% moisture content per the Brazilian standards for corn to be harvested or consumed; 16 samples had more than 15% moisture (8).

In Southern and Southeastern Brazil, the disease is seasonal and occurs mainly in the winter, when due to the low forage availability, the animals receive more supplementation with concentrates, including corn. However, outbreaks have been observed year-round (1,6,8,9). There are a few observations on the disease in tropical regions; of nine outbreaks reported from Pará, Paraíba, Mato Grosso, and Pernambuco (6,8,9), five occurred during the dry season and four during the rainy season.

The morbidity rate is 4-100%, and the fatality rate is nearly 100%, except in outbreaks reported in São Paulo (1) and Argentina (5), where 2 out of 11 and 1 of 7 horses, respectively, survived. The disease affects males and females of different ages (1, 2,5,8).

Clinical signs of MLEM are mainly associated with lesions in the cerebrum, including anorexia, somnolence or hyperexcitability, head pressing, circling, dullness, unilateral or bilateral blindness, focal seizures, and compulsive walking. However, other signs associated with lesions in the brain stem are also recorded, including impaired food prehension and mastication, ataxia, tremors, absence of palpebral reflex, decreased tongue and upper and lower lip tone, decreased sensibility of the face and palate, and mandibular slackening. Recumbence is also observed before death. The onset of clinical signs varies from 2 to 72 hours, but most affected horses die within 6-24 hours (8,9). Cases with a clinical course of up to 7-16 days can occur (1,2,6,8,9). Sudden death has also been reported (2,5). On some occasions, clinical signs appear up to 12 days after the withdrawal of corn from the diet (8).

At necropsy, most animals have cerebral lesions, but lesions in the brainstem are also observed, mainly in the thalamus and mesencephalon. One cerebral hemisphere is usually enlarged with flattened gyri. On the cut surface, there are yellow and hemorrhagic areas of malacia in the *centrum semiovale* and *corona radiata* of the cerebral hemispheres and internal capsule. Fluid-containing cavities are frequently observed within these areas. Hemorrhagic areas are occasionally observed in the thalamus, mesencephalic colliculi, cerebellar peduncles, pons, and medulla oblongata. Some lesions in the brainstem are probably secondary to compression due to edema. Lesions are usually unilateral but can be bilateral. After fixation, the yellow areas are less evident and the hemorrhagic lesions appear brown to gray (2,5,6,8,9,10

Histologic lesions consist of necrotic areas surrounded by edematous and hemorrhagic neuroparenchyma. Swollen astrocytes with eosinophilic cytoplasm and dark marginal nuclei (clasmadendrocytes) appear within the necrotic areas. Swollen vascular endothelium the vascular endothelium, perivascular edema, hemorrhages, and eosinophilic globules are also observed. Some vessels have perivascular cuffs consisting of eosinophils, neutrophils, or lymphocytes and plasma cells (2,5,6,8,9,10).

In the outbreak affecting the mule in this report, fumonisin concentration in the corn was 3 µg/g. However, because the sample was obtained from a batch other than that causing the disease, the concentration found might not be representative of the food consumed by the mules. Concentrations of fumonisin B1 in the corn in outbreaks of MLEM have been reported from 1.3 to 38.5 ug/kg (3,5,8,10).

The diagnosis is based on the history of consumption of corn or its by-products, the acute clinical signs, the typical macroscopic lesions, and the histology of the lesions. The fumonisin levels in the food are not necessary for the diagnosis but help in the diagnostic confirmation. Clinical signs can be similar to some clinical signs observed in poisoning by pyrrolizidine alkaloids-containing plants (*Crotalaria* spp and *Senecio* spp*.)* rabies, and equine encephalomyelitis, but the gross lesions are typical of MLEM and do not occur in these other diseases. Gross lesions of MLEM may be similar to those lesions observed in trypanosomiasis caused by *Trypanosoma evansi* (yellow areas of edema and malacia). Still, the clinical manifestation period of the disease (much longer in trypanosomiasis) and the histologic lesions allow for a differential diagnosis.

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