Multifocal polioencephalomyelomalacia in Simmental calves with elevated tissue aluminum and decreased tissue copper and manganese

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A spectrum of related malacic disorders called Simmental multifocal symmetrical encephalopathy have been reported in Simmental and Simmental crossbred cattle in Canada, Australia, and New Zealand. The cause of this condition is unknown. We describe multifocal polioencephalomyelomalacia in Simmental calves reared in Oregon, USA, with morphologic lesions similar to those described in Simmental multifocal symmetrical encephalopathy. These calves also had elevated tissue concentrations of aluminum and deficient hepatic copper and manganese concentrations, which may be related to this condition.

Four 7-month-old bull calves from a herd of 135 Simmental cows developed paresis, ataxia, and knuckling over of both hind limbs that progressed over a 2-month period to inability to rise. During the previous 2 years, 3 calves similarly affected died. Affected calves remained bright and alert and maintained the ability to suckle. Antibiotic therapy was not beneficial, and complete blood count and serum chemistry profiles were normal in the 3 calves evaluated. Two of the calves were presented to the Oregon State Veterinary Diagnostic Laboratory for postmortem examination.

Significant lesions were limited to the central nervous system, with secondary mild symmetrical atrophy of the rear limb muscles. Grossly, oblong to circular foci of malacia of various sizes (up to 1 cm diameter) were seen throughout the gray matter of the brain. Similar gross lesions were within the gray matter of the lumbar spinal cord in 1 of the calves. Microscopically, these lesions were cavitated and were composed almost entirely of necrotic debris (Fig. 1). Scattered viable neuroglial cells were within these foci but neurons were not observed. Microgliosis, astrocytosis (including gemistocytes), active neuronal necrosis, ischemic neuronal changes, and vasculitis were not observed. Vessels were prominent within the lesions, principally because of hypertrophy of endothelial nuclei. Neurofibrillar tangles and/or extensive demyelination were not observed in multiple Bodian- and Luxol fast blue-stained histologic sections. The histopathologic changes were markedly uniform throughout the affected foci.

The distribution of brain lesions was essentially identical in the 2 affected calves. The gray matter lesions of the brain involved numerous nuclei but invariably extended beyond nuclear boundaries. Individual lesions often involved more than 1 nucleus with some extension into the adjacent white matter. The thalamus and hippocampus were the most severely affected areas. Affected nuclei were hippocampus, caudate nucleus, putamen, ventrocaudal nucleus, medial and lateral geniculate bodies, interthalamic adhesion, hypothalamic nucleus, rostral and caudal colliculi, substantia nigra, pontine nucleus, caudal olivary nucleus, and accessory cuneate nucleus. Similar lesions were restricted to the dorsal gray horns, intermediate gray zone, and central gray substance of the lumbar segment of the spinal cord of 1 of the calves (Fig. 2). Although the lesions were bilaterally symmetrical in the spinal cord, bilateral symmetry of the brain lesions was not determined because one-half of each brain was utilized for toxicologic analyses.

Brain cholinesterase activity was normal, and chlorinated pesticides were not detected in the livers. An inductively coupled plasma (ICP) multielemental analysis was performed on tissues from both animals. Hepatic aluminum concentrations, 16.8 and 2.16 ppm, were elevated in both cases (bovine hepatic ICP aluminum frequency distribution: 91.6% < 2 ppm, 99.9% < 9 ppm; n = 782). Renal and brain aluminum concentrations were determined in the calf with the highest hepatic aluminum concentrations and were 2.220 ppm and 4.150 ppm, respectively. The renal concentrations were also elevated (bovine renal ICP aluminum frequency distribution: 95% < 2 ppm; n = 404). Brain concentrations are difficult to interpret because normal and abnormal concentrations have not been established. Because normal tissue aluminum concentrations are usually below the ICP limit of detection and because documented cases of aluminum intoxication (natural or experimental) in domestic animals are rare, normal and abnormal ranges for tissue aluminum concentrations are difficult to establish with certainty. In this case, frequency distributions provided the best measure of comparison between these elevated concentrations and those of the bovine population. Hepatic copper (3.090 and 13.3 ppm) manganese (0.214 and 1.430 ppm) were deficient (normal ranges: 25-100 ppm Cu and 2.5-6 ppm Mn). Other hepatic element concentrations in both calves were within normal ranges.

No source of aluminum exposure was found, and no toxic plants were identified on the premises. The affected calves were sired by genetically unrelated bulls. In 2 subsequent calving cycles, each calf received 200 mg of copper glycinate subcutaneously at birth, and no additional encephalopathy cases have been detected.

The pathogenesis of the lesions is difficult to determine. Lesions were predominantly confined to the gray matter; white matter changes were clearly secondary. The lesions were chronic, based upon the long duration of clinical signs, the size of the cavitated lesions, and the lack of severe in-
flamme in association with these lesions. Although glia were not necrotic within the lesions examined, the glia could have been affected in the acute phase. However, no lesions of a more acute phase were observed with which to determine either the type of neuronal necrosis or if glia were affected in earlier lesions. The age of these lesions precludes an accurate understanding of lesion progression that might provide clues to the pathogenesis of this disease.

Simmental and Simmental crossbred cattle from Australia and New Zealand have been described with multifocal symmetrical polioencephalomalacia with the proposed name Simmental multifocal symmetrical encephalopathy.3 Lesions in this condition are confined to the mesencephalon and rhombencephalon exclusive of the cerebellum; a distribution very similar to that of the brain lesions in the calves in this report. A Canadian herd of approximately 100 Simmental crossbred cattle has experienced 1-4 cases of polioencephalomalacia per year,3 similar to the incidence rate observed in the herd of the present report. A single calf from the Canadian report had poliomyelomalacia of the thoracic spinal cord. Distribution of the lesions in the brain and spinal gray matter were not described, but spinal lesions were reported as similar to lesions previously reported in Ayrshire calves. Spinal lesions of Ayrshire calves had a ventral horn

**Figure 1.** Focus of malacia in the gray matter of the lumbar spinal cord of a calf with polioencephalomyelomalacia involving the hypothalamic nucleus with mild spongiform change within adjacent white matter. Luxol fast blue counterstained with periodic acid-Schiff.

**Figure 2.** Malacia and neuronal necrosis within intermediate gray zone and central gray substance of the lumbar segment of the spinal cord of a calf with polioencephalomyelomalacia with mild spongiform change within adjacent white matter. Luxol fast blue counterstained with period acid-Schiff.
distribution, and there were no brain lesions. Similar lesions in Limousin cattle have been described throughout the brain, including the diencephalon and cerebellum.

Experimental dietary aluminum intoxication in conjunction with low dietary calcium in cynomolgus monkeys produced multifocal asymmetrical neuronal necrosis with scattered neurofibrillary tangles and minimal gliosis in the spinal cord ventral horn motor neurons, brain stem, substantia nigra, and motor cortex. Dialysis encephalopathy syndrome of humans, Alzheimer’s disease, amyotrophic lateral sclerosis, and Parkinson dementia of the western Pacific have also been associated with elevated tissue aluminum concentrations, although the interpretation of these associations remains controversial. These human neuropathies all center upon degenerative changes of various gray matter regions with the presence of neurofibrillary tangles. Major differences exist between both the human neuropathies, which have been associated with elevated aluminum, and experimental aluminum intoxication in monkeys as compared with the lesions of the present case. First, neurofibrillary tangles were not observed in Bodian-stained sections in these calves. Second, although the poliomyelomalacia present in the 1 affected calf involved the dorsal horns of the gray matter, experimental aluminum intoxication involves the ventral horns of the gray matter. Species differences might or might not account for these differences. Third, the bovine lesions in the spinal cord were bilaterally symmetrical, and although the symmetry of the brain lesions was unknown, the lesions of aluminum intoxication are asymmetrical. Fourth, cavitation and malacia are not features of aluminum intoxication in primates.

Aluminum intoxication is affected by interactions with other mineral imbalances. Both natural and experimental aluminum intoxication have been associated with low dietary calcium and magnesium. Hypomagnesemia and hypocalcemia induce secondary hyperparathyroidism in which parathyroid hormone enhances absorption and tissue disposition of aluminum. Manganese can substitute for magnesium in many biological reactions, and experimental elevations in dietary manganese exacerbate aluminum intoxication. Calcium and magnesium concentrations in serum and liver were within the lower normal limits in these calves, whereas hepatic copper and manganese concentrations were deficient. The significance of these alterations in mineral concentrations is unclear because these mineral imbalances have not been associated with aluminum intoxication in humans or monkeys.

Different diagnoses for encephalomalacia in domestic ruminants include laminar cerebral cortical necrosis diseases (polioencephalomalacia, lead intoxication, cyanide intoxication, and salt poisoning-water deprivation), which have a characteristic histopathologic appearance different from that seen in the calves of this report, the congenital form of copper deficiency, which is primarily a leukoencephalomalacia, and clostridial enterotoxemia in lambs, in which the lesions are generally confined to the internal capsule. Numerous vascular disorders, including infectious processes, can result in malacic states in any species; however, the chronicity of the disease process, lack of significant inflammation in the lesions, and distribution of the lesions in these calves argue against an infectious disorder. Although hepatic copper concentrations were deficient in these calves, the lesions of copper deficiency in young ruminants (noncongenital form) are predominantly hypomyelination and demyelination (due to inadequate cytochrome oxidase activity), lesions distinctly different from those observed in the calves of this report. Copper interacting with aluminum has not been reported.

These 2 cases do not establish a causative relationship between increased aluminum, decreased copper, and decreased manganese and the lesions observed. The morphologic changes observed in these calves have marked similarity to those seen in a series of malacic disorders previously reported in Simmental cattle. Genetic and metabolic disorders have been hypothesized as causes of these Simmental malacic disorders. However, the actual cause is unknown, and the roles of altered aluminum metabolism or other micronutrient imbalances have not but should be investigated, particularly in light of the favorable response of related animals to copper therapy. Whether these lesions represent a bovine variant of aluminum intoxication; a variant of ruminant copper deficiency; a pathologic process resulting from previously unreported interactions of aluminum, copper, and manganese; another portion of the spectrum of malacic disorders reported in Simmental cattle; or a combination of these factors is unknown.

References