Hypomyelination in the central nervous system has been described in calves, pigs, lambs, puppies, hamsters, rats, and mice.1,3,4 Strictly speaking, the term hypomyelination signifies defective myelin sheath formation, but the myelin present is of normal biochemical composition.2 In affected areas, axons are either thinly myelinated or nonmyelinated. The term dysmyelination signifies a similar situation, except that the myelin present is biochemically abnormal.2 In this study, hypomyelination is used to include both conditions because the critical morphologic expression of either is an inadequate quantity of myelin. Clinically, many animals with hypomyelination present in the neonatal period with whole body tremors, ataxia, and occasional seizures; hence, the common clinical designation of the syndrome as congenital tremors.1,2

Hypomyelination in the central nervous system is characterized by thin, discontinuous, and irregularly oriented myelinated axons.1,5 Myelin appears to be normal at birth, but the myelin present is not sufficient to achieve normal function.3,5 Myelination is a complex process that first begins in the brainstem in the hindbrain and extends centrifugally, reaching the telencephalon and diencephalon during the perinatal period. Myelination is prolonged into the neonatal period and is completed by 8 weeks of age.6 At the time of birth, myelination is complete in the caudal medulla, cervical spinal cord, and cranial nerves. Myelination of the cerebellum begins at about 15 days of gestation and extends cephalad through the rostral pons to the cerebellar cortex in the neonatal period.4

Hypomyelination presents specific difficulties for ultrastructural and immunohistochemical analysis. The quality of wax-impregnated and paraffin-embedded preparatory procedures is important in defining the myelin characteristics.1,5 We used a limited supply of paraffin-embedded tissues and electron micrograph negatives for this study. Tissues and electron micrograph negatives for this study were retrieved from the archives of the Anatomy Department of the New York State College of Veterinary Medicine (NYSCVM) at Cornell University (circa 1983), and from the archives of the Neurology Service of the New York State College of Veterinary Medicine (NYSCVM) at Cornell University (circa 1983). The GFAP stain was performed with rabbit anti-GFAP at a 1:320 dilution, the MAG stain with mouse anti-leu 7 at a 1:500 dilution, and the PLP technique with rabbit anti-PLP at a 1:100 dilution. Tissues collected at necropsy included brain, spinal cord, heart, lung, liver, kidney, adrenal gland, spinal (peripheral) nerve rootlets and attached ganglia, spleen, skin, and gastrointestinal tract tissues and appropriate serum controls were run. No trypsinization of tissues was required, and the sequential sections were also stained using an indirect immunoperoxidase streptavidin biotin technique (Zymed Streptavidin–Biotin System®, Zymed Laboratories, San Francisco, CA). The method of Wasserman et al.1 was used with the following primary antibodies: glial fibrillary acidic protein (GFAP, Biomeda Co., Foster City, CA), myelin basic protein (MBP, a gift from Dr. C. del Cerro, Rochester, NY), myelin-associated glycoprotein (MAG, stained with anti-leu 7, Becton Dickinson Co., Mountain View, CA), and proteolipid protein (PLP, a gift from Drs. J.-M. Matthieu, Switzerland and T. V. van Wachnedt, Germany). The GFAP stain was performed with rabbit anti-GFAP at a 1:320 dilution, the MBP technique with rabbit anti-MBP at a 1:516 dilution, the MAG stain with mouse anti-leu 7 at a 1:100 dilution, and the PLP technique with rabbit anti-PLP at a 1:500 dilution.

Case records and a limited supply of paraffin-embedded tissues and electron micrograph negatives for this study were retrieved from the archives of the Anatomy Department of the New York State College of Veterinary Medicine (NYSCVM) at Cornell University (circa 1983). A litter of five kittens from the same queen and tom (female and one of undetermined sex) were clinically normal at birth. The two surviving kittens (one male and one of undetermined sex) were clinically normal until 4 weeks of age, when they developed progressively intensive whole body (action) tremors accompanied by episodes of frenzied behavior with indiscriminant biting. Two kittens died of unknown causes at 2 days of age (no necropsy examination was performed). The two surviving kittens revealed a quiet (normal) state at rest, but with activity, clinical signs as described above became evident. Differential diagnoses of storage disease or hypomyelination were considered. The Siamese kittens (Nos. 1, 2) were euthanatized with intravenous barbiturate (Soccumb®, Anthony Products, Arcadia, CA) at 6 weeks of age; a 6-week-old healthy female domestic shorthair kitten (No. 3) served as a control. Tissues were normal. The two afflicted kittens were noted to the New York State College of Veterinary Medicine (NYSCVM) at Cornell University (circa 1983). A litter of three Siamese kittens was apparently normal at birth. One kitten died of unknown causes at 2 days of age (no necropsy examination was performed). The two surviving kittens (one male and one of undetermined sex) were clinically normal until 4 weeks of age, when they developed progressively intensive whole body (action) tremors accompanied by episodes of frenzied behavior with indiscriminant biting. Two previous litters of five kittens from the same queen and tom were normal. The two afflicted kittens were noted to the neurology service of the NYSCVM. Neurologic examination of both kittens revealed a quiet (normal) state at rest, but with activity, clinical signs as described above became evident. Differential diagnoses of storage disease or hypomyelination were considered.
Fig. 1. Transverse section. Caudal lumbar spinal cord; kitten No. 1. Note the marked deficiency of myelin in the lateral and ventral funiculi compared with normal myelin in the dorsal funiculus. Luxol fast blue-cresyl violet. Bar = 1 mm.

Samples of white matter (specific sites unknown) from the cerebral frontal lobe and from the lateral funiculus of the thoracolumbar spinal cord (kitten Nos. 1, 3) were removed from 10% neutral buffered formalin, cut into 3-mm³ blocks, transferred to 1% glutaraldehyde/1% paraformaldehyde, washed in 0.1 M phosphate buffer at pH 7.4, post-fixed in Dalton’s chrome-osmium tetroxide, dehydrated, and embedded in Epon-araldite. Thick sections, cut at 1 μm, were stained with toluidine blue and basic fuchsin. Thin sections, cut at 90 nm, were stained with uranyl acetate and lead citrate and examined in a Philips 201 electron microscope at 80 kV. Only a limited number of archived electron micrograph negatives of the Siamese kittens were available for examination (there were no embedded plastic blocks to section or formalin-fixed tissues to process).

There were no abnormalities detected in the affected or control kittens on gross examinations. Histologic examination of spinal cord from both Siamese kittens revealed marked pallor of white matter (deficiency of myelin) of the lateral and ventral funiculi of the spinal cord with no evident rostrocaudal gradation in severity. The dorsal columns of the spinal cord appeared normal. The myelin of dorsal and ventral rootlets and the attached spinal ganglia stained normally. The appearance of the brain stem, cerebellar, and cerebral sections was similar to that of the control tissues. Kitten No. 2 was much less severely affected than was its littermate (No. 1). The myelin deficit was best demonstrated by the LFB stain (Fig. 1). Holmes’ silver staining revealed morphologically normal axons in all sections examined.

There was a mild increase in astroglia (cell bodies and processes) in hypomyelinated regions of the spinal cord in the affected kittens, as seen in HE-stained sections. The numbers of oligodendrocytes and microglial cells appeared normal.

GFAP staining confirmed a mild astrogliosis, including an increased prominence of the glia limitans in the hypomyelinated areas of the affected kittens; astrogial processes often assumed a radial orientation. MBP, MAG, and PLP staining were of comparable stain intensity in the afflicted kittens and the control, although chromagen was less dense in the hypomyelinated areas, reflecting the increased numbers of hypomyelinated axons.

Electron micrographs of the myelin-deficient areas of the spinal cord white matter (kitten No. 1) revealed a preponderance of nonmyelinated axons, and the few myelin sheaths that were present were thin and often poorly compacted (Figs. 2, 3). The lack of sufficient material prevented any quantitative assessment of glial cells, although randomly observed oligodendroglial cells were unable to produce and/or maintain normal myelin on occasional associated axons (Fig. 4).

At the cellular level, hypomyelination of the central nervous system (CNS) may reflect primary disorders in oligodendrocytes, axons, astrocytes, or a combination thereof. Possible oligodendrocytic deficits include a failure of precursor cell division, inability of immature cells to migrate and make contact with axons, abnormal maturation, or early...
cell death. Possible axon anomalies would include failure to attain a critical diameter or to generate a signal for myelination. Astrocytes may be involved if their processes abnormally surround and invest axons, thereby prohibiting oligodendrocyte/axon interaction. Type 2 astrocytes may also be required for normal myelination. The Siamese kittens did have variably increased numbers of astroglia, which may have surrounded and interfered with normal oligodendrocyte and axon interaction.

The presence of abnormal CNS myelin with concurrent normal peripheral nervous system (PNS) myelin reflects two distinct myelin-producing cell populations: Schwann cells of neural crest origin producing PNS myelin, and oligodendroglial cells of neuroectodermal origin produce CNS myelin. In addition to histogenetic differences, Schwann cells depend on extracellular matrix for PNS myelin production (whereas oligodendrocytes do not), and Schwann cells invest single axons whereas oligodendrocytes can produce and sustain up to 50 myelin internodes.

Defects in feline myelinogenesis are apparently extremely rare. There is a report of two 7-week-old Egyptian Mau kittens that developed progressive ataxia and hypermetria with "periodic 'epileptiform' fits." Although the signalments and clinical history are similar to those of the Siamese kittens, the morphologic lesions consisted of extensive brain and spinal cord vacuolation ("spongy degeneration"), specifically resulting from vacuolation within myelin sheaths. Such spongy degeneration was not present in the Siamese kittens.

The delayed onset of clinical signs (4 weeks) in these kittens is similar to the delay noted in the myelin-deficient rat (12 to 15 days), myelin deficient hamster\(^1\) (14 days), shi\(^{\text{mid}}\) mouse\(^2\) (12 days), myelin synthesis-deficient mouse\(^3\) (11 days), Weimaraner dog (1 to 3 weeks), Springer Spaniel dog (10 to 12 days), Lurcher dog (2 weeks), and Samoyed dog (3 weeks). The significance of this delay as opposed to the abrupt neonatal onset of signs in swine, sheep, calves, and the Chow Chow and Dalmatian dogs is unknown.

The frenzied behavior with indiscriminant biting in these kittens is unusual for hypomyelination and may represent paresthesia evoked by inappropriate excitation of noninnervated portions of sensory pathways. Similar behavior has not been noted in other species with hypomyelination, although the myelin-deficient rat and the myelin synthesis-deficient mouse develop lethal seizures.

Viral infections, genetic defects, intoxications, or (by elimination) idiopathic factors can produce hypomyelination. The cause of hypomyelination in these kittens could not be determined. The lack of affected offspring in previous litters from the same breeding pair would argue against a genetic etiology (unfortunately, the breeding pair is unable for further study). The cattery from which the kittens came was unable to identify any potential environmental toxin(s), and no feline viruses have been implicated in this type of disease to date, although in utero or early neonatal infection with feline panleukopenia or feline leukemia viruses remains a possibility. Process of elimination indicates that these kittens had idiopathic hypomyelination. This is the first report of CNS hypomyelination in the kitten. Clinicians and pathologists should consider this disease when confronted with neonatal to young kittens with "congenital tremors."

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References

Hyperplastic Gastritis with Intraepithelial *Campylobacter*-like Organisms in a Beagle Dog

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**Key words:** *Campylobacter*-like organism; CLO; dogs; hyperplastic gastritis.

Chronic hypertrophic gastritis, proliferative gastritis, or hyperplastic gastritis are generic terms in dogs for rare conditions characterized by a marked thickening of gastric rugae due to mucosal hyperplasia. The lesions may predominantly involve the mucosa of the body of the stomach, as in Meetier’s disease in human beings, or the antral mucosa, as the name antral pyloric hypertrophy syndrome implies. Similar gastric lesions have been seen as isolated findings, in Zollinger-Ellison syndrome, as part of the gastrointestinal disease affecting Basenji dogs and dogs with mast cell tumors. The causes are unknown; however, immune or hormonal disorders, environmental factors, and genetic predispositions may be involved in the pathogenesis.

A 6-month-old female Beagle dog was received from Marshall Farms (North Rose, NY) as part of a group of dogs intended to be used in drug safety studies. The dog was clinically normal upon arrival but was euthanatized after a 1-month period of weight loss (loss of 2.5 kg), loss of appetite, and soft feces that commenced 10 days after arrival. The only significant necropsy finding was a marked diffuse thickening of the pyloric antral mucosa, sharply demarcated from the normal mucosa of the stomach and proximal duodenum. The enlarged rugae were about 7 mm thick, smooth, and yellow and had multifocal areas of mild congestion or hemorrhage (Fig. 1).

Tissues were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin. Sections from the stomach were also stained with the periodic acid–Schiff (PAS) technique and by a modified Warthin-Starry silver impregnation. Deparaffinized sections of the stomach were tested by indirect immunofluorescence using polyclonal rabbit antiserum (1080176) that reacts to the intracellular *Campylobacter*-like organism (CLO) omega antigen in proliferative intestinal lesions in swine, hamsters, ferrets, and rabbits. The sections were stained with fluorescein-conjugated sheep anti-rabbit immunoglobulin and examined with a Zeiss EM109 electron microscope. Controls included normal Beagle dog stomachs, normal ferret colons, and tissues from ferrets with proliferative colitis. Formalin-fixed portions of the stomach were divided into 1-mm² sections, immersed in 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.37), post-fixed in 2% osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with a Zeiss EM109 electron microscope.

Histologically, the gastric lesion was confined to the mucosa which was about 3 mm thick as a result of a marked diffuse glandular hyperplasia and a mild crypt branching (Fig. 2). The glands were crowded in the lamina propria but did not penetrate the muscularis mucosa. A few glands were slightly dilated and contained eosinophilic debris. The lamina propria was diffusely infiltrated by some plasmocytes and fewer macrophages or lymphocytes. The hyperplastic glandular epithelium was composed of columnar to high columnar, slightly basophilic cells. Their oval to elongated clear nuclei were in the basal portion of the cells and contained up to three round eosinophilic nucleoli. Numerous mitoses and individual necrotic cells were observed. The hyperplastic cells contained a variable amount of PAS-positive material. The fundus and other organs, including the intestine, were unremarkable. Warthin-Starry staining revealed numerous curved or short bacteria in the apical cytoplasm or at the surface of hyperplastic glandular cells (Fig. 2) and admixed with necrotic debris in dilated glandular lumens. Clusters of organisms were also observed within the cytoplasm of a few macrophages in the lamina propria near the luminal surface. In addition, a few larger and spiral-shaped organisms were occasionally seen in the glandular lumens of both the hyperplastic region and the fundus. After indirect immunofluorescence staining with omega 1080/76 antiserum, numerous fluorescent organisms were seen in the apical cytoplasm of the hyperplastic cells and formed densely globoid structures in some areas. Macrophages in the lamina propria were occasionally labeled with fluorescent material. The immunofluorescence assay was strongly positive in ferret proliferative colitis, but no fluorescence was seen in normal ferret colon. There was no fluorescence in the control dog stomach, although large gastric spiral organisms were found with Warthin-Starry staining.

Transmission electron microscopic examination con-