Congenital hypomyelination neuropathy is a rare condition in all species, including human beings. In the veterinary literature relating to domestic animals, there is only a single report, which involved two Golden Retriever puppies in a litter of seven. The present report is the first of a congenital hypomyelination neuropathy in a lamb.

A 2-month-old Dorset ewe lamb was donated to the Virginia Tech Veterinary Teaching Hospital because of incoordination. The lamb was one of a set of twins. The lamb had had intermittent tremors and incoordination of the head and limbs since birth. The other twin was clinically normal. At admission, the lamb was alert, appettent, and thin and weighed 6.3 kg. Temperature and pulse were normal, but there was tachypnea (70/minute) and coughing. Auscultation of the thorax revealed harsh bronchovesicular sounds over left and right lung fields. There was no menace response in either eye, but pupillary light reflexes were normal. Ophthalmic examination revealed small colobomas in both eyes. Intention tremor of the head occurred during prehension. The lamb was able to stand with assistance. Its gait was abnormal with ataxia and hypermetria in all limbs. Strength and conscious proprioception appeared normal in all four limbs. Patellar reflexes were absent bilaterally. The results of a complete blood count were normal. Cerebrospinal fluid sampled from the atlanto-occipital and lumbosacral spaces contained increased protein (146 and 403 mg/dl, respectively) and a marginal increase in mononuclear cells (11/µl and 6/µl, respectively). Antibodies against bovine viral diarrhea virus were detected in a blood sample taken at admission (1:64) and in a blood sample taken 3 weeks later (1:32). No

![Fig. 1. Electron micrograph. Tibial nerve; control lamb. Normally myelinated fibers of different calibers are present. Uranyl acetate and lead citrate. Bar = 3 µm.](image1)

![Fig. 2. Electron micrograph. Tibial nerve; affected lamb. Most fibers present are amyelinated. Uranyl acetate and lead citrate. Bar = 3 µm.](image2)
antibodies against blue tongue virus were detected in serum. Electromyographic examination of skeletal muscle was normal, but motor nerve conduction velocities could not be determined because of absence of evoked muscle action potentials.

The affected lamb and an age-matched control lamb were euthanatized by barbiturate overdose and subjected to routine postmortem examination. Samples of brain, spinal cord, peripheral nerves (radial, median, ulnar, sciatic, and tibial), and skeletal muscle were fixed in 10% neutral buffered formalin and embedded in paraffin. Fresh, frozen muscle samples were taken for histochemical analysis. Nerve samples from the control lamb were fixed in 2.5% glutaraldehyde in Millonig phosphate buffer (pH 7.3). Nerve samples from affected and control lambs were post-fixed and stained in 1% osmium tetroxide; one half of each nerve was processed for single-fiber teasing and the other half was processed through a series of graded ethanol solutions for Epon embedment.

No abnormalities were noted on gross inspection of tissues. Sections of brain and spinal cord were normal except for absence of myelin staining (using Luxol fast blue) in the nerve root exit-entry zones. No abnormalities were observed in skeletal muscle samples. Pronounced abnormalities were present in cross sections of peripheral nerves: most axons were amylinated (without myelin sheaths) or hypomyelinated (surrounded by very thin myelin sheaths). Axonal necrosis was not seen, and there was no visual evidence of nerve fiber loss. No attempt was made to quantify nerve fiber diameters or fiber density because different fixatives were used on affected and control peripheral nerve samples. Individual teased fibers were difficult to prepare and identify because of the lightness of myelin staining with osmium tetroxide; however, there was no evidence of paranodal or segmental demyelination. Ultrastructural examination confirmed that nearly all nerve fibers were either amylinated or had markedly reduced numbers of myelin lamellae, and there were increased numbers of Schwann cell nuclei, as compared with controls (Figs. 1, 2). The maximum number of myelin lamellae counted in any fiber was 12 (in control nerves, myelin lamellar counts ranged from 15 to 20 in small caliber fibers to more than 150 in larger fibers). The number of neurofilaments appeared increased in many axons, irrespective of fiber caliber. Other axonal and Schwann cell organelles appeared normal. Many axons were surronded by redundant basement membranes, which frequently formed “necklaces” around hypomyelinated, amylinated, and unmyelinated fi-
bers (Fig. 3). Occasional axons were surrounded by one or two lamellae of loose or uncompacted myelin, usually with intervening loops of Schwann cell cytoplasm. Basement membrane directly abutted the axolemma in many amylinated fibers (Fig. 4), whereas in others, a thin loop of Schwann cell cytoplasm separated these two membranes. Occasionally, electron-dense subaxolemmal material was seen in amylinated fibers (Fig. 4). There was no evidence of myelinoaxonal necrosis, onion bulb formation, denervated Schwann cells (Bungner bands), or macrophage infiltration. Unmyelinated fibers appeared normal. Endoneurial collagen was increased, and dark-staining endoneurial fibroblasts were sometimes seen.

This is only the second report of congenital hypomyelination involving peripheral nerves in domestic animals and is the first in sheep. The cause of the hypomyelination was not determined. Abnormal myelination of the central nervous system has been reported in a variety of animal species, usually associated with hereditary or infectious agents. In sheep, hypomyelination of the central nervous system is known to occur with Border disease, a congenital disorder caused by a pestivirus. Peripheral nerve myelin is normal in affected sheep.

The morphologic appearance of nerves from the affected lamb was similar to that described recently in two Golden Retriever littermates with congenital hypomyelination neuropathy. In both species, hypomyelination involved fibers of all caliber, there was an apparent increase in numbers of axonal neurofilaments as compared with controls, active myelin breakdown was not a feature, and there was no evidence of inflammatory infiltrates. In this lamb, however, many more amylated fibers and redundant basement membrane “necklaces” around small- and large-caliber fibers were seen. The morphologic appearance of the lamb peripheral nerve was also similar to that described in children with congenital hypomyelination neuropathy, a subgroup of the hereditary motor and sensory neuropathies (HMSN), in which congenital impairment in myelin formation, without myelin degeneration, has been postulated. In congenital hypomyelination neuropathy in children, there appears to be a spectrum of morphologic abnormalities associated with these redundant basement membranes, ranging from amylination of virtually all axons, to hypomyelination without demyelination, to hypomyelination with varying degrees of myelin breakdown, sometimes with hypermyelination. Although demyelination was not evident in nerves from this lamb, this reduplication of basement membrane simulated primitive onion bulb formation because the membranes rarely contained leaflets of Schwann cell cytoplasm. In children with congenital hypomyelination neuropathy, the hypomyelination may occur secondary to a Schwann cell defect, and the excess proliferation of these membranes may result from abnormal axon–Schwann cell signalling. Results of research studies on several genetic mouse mutants in which there is peripheral nerve hypomyelination confirm complex interactions between Schwann cells and axons.

The elevated cerebrospinal fluid protein seen in the affected lamb reportedly is also a feature of congenital hypomyelination neuropathy in children.

References
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