Acral Mutilation and Nociceptive Loss in English Pointer Dogs*

A Canine Sensory Neuropathy

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Summary. Acral mutilation and analgesia occurred in three of a litter of nine pups produced by a mating of clinically normal English Pointer dogs. Post-mortem studies on one of the affected pups revealed changes at the level of the primary sensory neuron which included: a reduction in spinal ganglia size, a 22–50% deficiency of ganglionic neurons, and a disproportionately large population of small sensory cell bodies. The only change noted in the spinal cord occurred in the dorsolateral fasciculus where reduced fiber density appeared to correlate well with the observed nociceptive defect. Light- and electron-microscopic examination of spinal roots, ganglia, and peripheral nerves provided evidence of myelinated and unmyelinated fiber degeneration. The neuronal degeneration, however, appeared quantitatively inadequate to account for the deficiency of sensory cell bodies. It was concluded that this mutilating acropathy was a manifestation of a sensory neuropathy in which the neuronal deficiency resulted from insufficient development and slowly progressive, postnatal degeneration.

The clinical and pathologic findings in this canine disorder were compared with those reported in hereditary sensory neuropathies of man and other animals.

Key words: Comparative neuropathology — Canine sensory neuropathy

In man, insensitivity to pain and mutilation of the acral portions of the extremities occur in certain inherited disorders that selectively or heavily affect the development and/or survival of the primary sensory neurons. These disorders have been classified on clinical and pathologic bases into four types of hereditary sensory neuropathy (HSN) and distinguished from syringomyelia and other diseases characterized by mutilation (Dyck and Ohta 1975). Despite these recent nosologic distinctions, the pathogenetic mechanisms of these neuropathies remain obscure (Asbury and Johnson 1978).

Recently, a search for comparable spontaneous nociceptive disorders in animals was undertaken in an effort to identify models for study of the pathogenesis of human sensory neuropathies (Cummings 1979). Two hereditary sensory neuropathies, dystonia musculorum and “sprawling”, have been identified in mice (Duchen et al. 1964; Janota 1972; Duchen and Scaravilli 1977a, b; Duchen 1979). In these, however, the prominent clinical feature was sensory ataxia rather than analgesia and mutilation. More recently, Jacobs et al. (1980) have described a spontaneous neurologic mutation of Sprague-Dawley rats wherein ataxia is accompanied by reddening, ulceration, and mutilation of the feet.

An unusual, recessively inherited condition marked by acral mutilation and insensitivity has been reported in Shorthaired Pointer dogs (Sanda et al. 1964; Pivnik 1973). This breed-specific disorder has been called “toe necrosis”, hereditary neurotrophic osteopathy, and ulcer-o-mutilating acropathy (Pivnik 1973). Affected pups, at 4 months of age, began to lick and later bite their paws. Autoamputation of the digits often resulted. The superficial sensitivity of the limbs was reduced and the mutilated portions of the extremities were totally insensitive to painful stimuli (e.g., pin prick, surgical incision, and heat applications). Affected dogs walked on the severely mutilated paws without evidence of lameness or ataxia. Pivnik (1973) found that previously reported spinal funicular degeneration was an inconsistent pathologic change. He has perceived this canine disorder as a hereditary acrodystrophic neuropathy and has concentrated on

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the spinal roots, peripheral nerves, and nerve endings as more likely sites for the pathologic process.

In this report we describe similar acral mutilation and insensitivity to pain in English Pointer dogs and attribute this acropathy to pathologic changes affecting the primary sensory neuron.

Case Report

A 4.5-month-old female English Pointer dog was referred to the Teaching Hospital at the New York State College of Veterinary Medicine because of progressive mutilation of the distal portions of the extremities. The owner, a dog breeder, reported that the proposita and two other affected pups (a male and a female) were members of a litter of nine from a breeding of clinically normal parents. These three pups were notably smaller than their littermates at 11–12 weeks of age when they suddenly began to lick and bite their paws.

On admission, the proposita walked unhesitantly on severely mutilated paws. The left hind paw was involved most extensively. The distal phalanges of the third and fourth digits were lost and replaced by granulation tissue. The entire paw was swollen and paronychia was prominent on the second and fifth digits. On the plantar surface, the metatarsal pad was deeply ulcerated and the skin over the tuber calcis was thinly haired and lacerated. The phalanges remained intact on the right hind paw, but paronychia occurred on all digits and plantar ulcers eroded the metacarpal and fourth digital pads. The digits of the forelimbs were variously affected by paronychia, nail reduction or loss and pad ulceration. Both the superficial cervical and popliteal lymph nodes were enlarged.

The animal was totally unresponsive when painful stimuli (pin prick and forceps compression) were applied to the digital regions of the hind paws. These stimuli provoked no reaction when applied to the inflamed and ulcerated regions of the forepaws, although the dog withdrew and vocalized when intact regions of the forepaws were stimulated. Tendon reflexes were preserved. There was no evidence of motor or autonomic impairment. Electromyographic studies on the proximal and distal muscles of the limbs revealed no denervation potentials. Sensory and motor ulnar nerve conduction velocities of 47 and 44 m/s, respectively, were considered to be within normal limits for dogs of this age.

Attempts to prevent further mutilation with bandages or restraining collars met with only limited success, and the animal was euthanatized at 5 months of age at the request of the owner.

The other two affected littermates were not available to us for study. These animals, however, were thoroughly examined at 4 months of age at another hospital and these evaluations were forwarded. As in the case of the proposita, acral mutilation was prominent in both of these pups. Loss of thermal and pain sensations was reported to extend proximally over the limbs to include part of the trunk. No proprioceptive loss was detected, and tendon reflexes remained intact. Electromyographic and motor nerve conduction velocity studies disclosed no abnormalities. Soon after their clinical evaluations, both pups were euthanatized at the owner’s request, and tissues were not made available for study.

Material and Methods

The proposita was heparinized prior to i. v. administration of a lethal dose of pentobarbital sodium. A fixative solution containing 1% glutaraldehyde, 1% paraformaldehyde, phosphate-buffered to pH 7.2 was then perfused at 120 mm of Hg via the left cardiac ventricle. The brain, spinal cord, spinal roots, and proximal and distal lengths of the peripheral nerves were removed along with samples of the major organs and acral skin lesions and stored in fixative. Blocks cut from the brain, spinal cord, and other organs, as well as selected spinal roots, ganglia, and peripheral nerves were embedded in paraffin and sectioned at 8 μm. Luxol fast blue-cresyl echt violet, Holmes silver, and hematoxylin and eosin (H.-E.) stains were applied to sections of nervous tissue; other organs were stained with H.-E.

One to two-centimeter lengths of lumbar spinal roots and peripheral nerves were immersed for 1 week in a 1% solution of osmium tetroxide. These lengths were then transferred to glycerine or Epon and teased apart with fine needles in order to isolate individual myelinated fibers.

Cervical, thoracic, and lumbar spinal ganglia, spinal roots, and peripheral nerves were trimmed, postfixed in Dalton’s chrome-osmium tetroxide, then dehydrated, and embedded in Epon-Araldit. Semi-thin sections, cut at 1 μm, were stained with toluidine blue alone or in a combination with basic fuchsin. Thin sections, approximately 90 nm-thick, were stained with uranyl acetate and lead citrate and examined at 80 kV with a Philips 201 electron microscope.

A clinically normal English Setter dog, 3 weeks younger than the proposita, but comparable in weight and confirmation, was necropsied according to the aforementioned techniques. Tissues from this dog served as a control for subsequent light- and electron-microscopic investigations. Spinal ganglia (C5, C6, T1, L5, and L-) were isolated from the dorsal roots of the affected and control animals and weighed on a Mettler balance.

Each of these ganglia subsequently was embedded in paraffin. Sections were cut serially at 10 μm in the longitudinal plane, mounted in order, and stained with H.-E. The total number of 10-μm sections prepared from each ganglion was determined. The nucleoli of nerve cell bodies were counted on those sections that fell at intervals of 10% of the total number of sections. Counts were performed with an eyepiece reticule according to the procedure of Pearson et al. (1978). The neuron population in each ganglion was calculated by the formula N (total number of neurons) = n (number of nucleoli in sections sampled) × P (sample section frequency). A correction for split nucleoli (Konigsmark 1970) was applied by the formula $t = \frac{t}{t + d}$ ($t$ = section thickness; $d$ = mean nucleolar diameter).

Neuron diameters were measured with a stage micrometer-calibrated ocular in the C6 and L4 spinal ganglia of the affected and control dogs. Diameters of 1,000 neurons were measured in each ganglion using sections in the series that fell at intervals of 20% of the total number of sections.

Results

Pathology

Macroscopic Findings. The only change detected grossly at necropsy was a decrease in prominence of the spinal ganglia and dorsal roots. The decrease was most obvious in the ganglia associated with the intumesences. The weights of five ganglia isolated from the proposita and the control dog are contrasted in Table 1.

Light-microscopic Findings. The nerve cell bodies in the spinal ganglia of the dog normally are concentrated in a subcapsular mantle zone (Scharf 1958). This mantle concentration was apparent in the control dog’s ganglia where neurons were densely packed in a series of rows. In the ganglia of the affected dog, however, the neuron mantle was generally decreased in thickness, and at many points the cell bodies within the mantle were loosely arranged (Fig. 1a). At these points the widened