A 4-year-old spayed-female Golden Retriever was evaluated at The Ohio State University Veterinary Medical Center for multiple cranial nerve deficits. Two months previously, the dog presented to the referring veterinarian for difficulty closing the jaw. A presumptive diagnosis of trigeminal neuritis was made. No treatment was initiated. Over the next 3–5 weeks, the dog was able to close the jaw, but continued to have difficulty chewing food. During this time mydriasis developed in both eyes (OU) and the dog became light sensitive. A week before presentation, the dog developed difficulty swallowing and frequently would gag and produce a very thick, viscus material throughout the day. No vomiting or regurgitation was observed. Bilateral temporals and masseter muscle atrophy also was noted and progressed over the previous 2 months. No medications had been prescribed at the time of presentation, and the dog had been otherwise healthy before the onset of clinical signs.

On physical examination, no abnormalities were noted except for bilaterally symmetric atrophy of the temporals and masseter muscles. The dog retched up a thick, yellow foam during the examination and would make several attempts when swallowing saliva. On neurologic examination, an intermittent right-sided head tilt was noted. The gait examination was normal with no ataxia or weakness. Cranial nerve examination identified mydriasis OU, absent direct and consensual pupillary light reflexes (PLR), ventral strabismus of the right eye (OD), absent nasal sensation bilaterally, absent sensation at the base of both ears, and absent facial sensation except at the upper lip margins. All other cranial nerve reflexes including menace, oculocephalic, and gag reflexes were normal. All postural reactions and spinal reflexes were normal and no pain was elicited on spinal palpation.

The finding of a right-sided head tilt and ventral strabismus OD was indicative of vestibulocochlear nerve (sensory dysfunction) involvement, whereas mydriasis OU and absent direct and indirect PLR OU suggested involvement of the oculomotor nerve, more specifically, an autonomic (parasympathetic) dysfunction. Both sensory and motor components of the mandibular branch of the trigeminal nerve, as well as the sensory component of the maxillary and ophthalmic branch, were thought to be affected because of absent nasal sensation bilaterally, atrophy of the temporals and masseter muscles, and absent sensation at the medial and lateral canthi of the eye as well as at the base of the ear. The lack of facial sensation also was suggestive of dysfunction of the maxillary branch of the trigeminal nerve, whereas difficulty swallowing was indicative of dysfunction of the glossopharyngeal, vagus nerve, or both. Based on the neurologic examination, a cranial neuropathy affecting the autonomic, sensory, and motor systems was suspected. An ophthalmologic examination was performed and revealed fixed and dilated pupils OU, confirming parasympathetic involvement of the oculomotor nerve. The Schirmer tear test was within normal limits bilaterally, indicating normal parasympathetic function of the facial nerve.

A CBC, biochemistry profile, and thyroid function tests were performed. Abnormalities on biochemistry included hypophosphatemia (2.6 mg/dL; reference range, 3.2–8.1), and hypokalemia (3.75 mEq/L; reference range, 4.2–5.4). Evaluation of CBC indicated increased protein concentration (7.8 g/dL; reference range, 5.0–7.2), mild leukocytosis (15.6×10⁹/L; reference range, 4.1–15.2) with mature neutrophilia (14.0×10⁹/L; reference range, 3.0–10.4), and lymphopenia (0.6×10⁹/L; reference range, 1.0–4.6). These findings were consistent with a stress leukogram. All thyroid function tests were within normal limits.

Moderate megaesophagus involving the caudal cervical and entire thoracic esophageal regions was observed on thoracic radiographs, and was judged to be caused by vagal nerve dysfunction. Abdominal ultrasound examination was unremarkable. Electrodagnostic testing, including electromyography and measurement of motor and sensory nerve conduction velocities, as well as nerve and muscle biopsies were offered, but declined by the
No improvement was noted over the ensuing 3 days. The dog continued to have difficulty eating and swallowing and was euthanized.

A postmortem examination was performed and no gross abnormalities were observed except for the previously noted bilateral atrophy of the temporalis and masseter muscles. Histopathology of the brain (frontal cortex, parietal cortex, hippocampus, mesencephalon, cerebellum, pons, and medulla) did not reveal any lesions of the neuropil or neuronal cell bodies. All lesions were confined to the nerve fibers. Samples of the optic, oculomotor, trochlear, trigeminal (mandibular, maxillary, and ophthalmic branches), abducens, facial, vestibulocochlear, glossopharyngeal, vagus, and hypoglossal nerves, as well as sections from the sciatic and radial nerves, were collected. Nerve specimens were either fixed in 10% neutral-buffered formalin or unfixed and frozen in isopentane precooled in liquid nitrogen. Fixed specimens

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**Fig 1.** Paraffin (a,b) and plastic embedded sections (c–e) from the mandibular branch of the trigeminal nerve (a,b), glossopharyngeal nerve (c) and oculomotor nerve (d,e) are shown. Marked nerve fiber loss and fibrosis (b) is evident in all three nerves with diffusely scattered mononuclear cell infiltrations within the endoneurium. As shown in (b) and (d), nerve fascicles can be variably affected with a fascicle containing a subjectively normal density of myelinated nerve fibers (left in d) adjacent to a fascicle containing a marked depletion of myelinated fibers (asterisk in b, on the right in d and shown at higher power in e). Electron microscopic examination of unmyelinated fibers from the oculomotor nerve (f) showed they were unaffected (long arrow points to a Remak cell nucleus and shorter arrow highlights 2 small myelinated fibers). Hematoxylin and eosin stain in (a), Masson’s trichrome stain in (b), toluidine blue-basic fuchsin stain in (c), and toluidine blue stain in (d,e). Bar = 0.53 μm for (e).
were embedded in both paraffin and plastic resin by established procedures. Paraffin sections were cut (5 μm) and stained with hematoxylin and eosin (H&E) and Masson’s trichrome, and plastic sections were cut (1 μm) and stained with toluidine blue, for evaluation by standard light microscopy. For ultrastructural evaluation, thin plastic sections (60–90 nm) were cut with a diamond knife and stained with uranyl acetate and lead citrate before electron microscopic examination.

Specimens were collected from the temporalis, masseter, and extensor carpi radialis muscles on the left and right side of the body. Unfixed samples were flash frozen in isopentane precooled in liquid nitrogen and then stored at −80°C until further processed by a standard panel of histological and histochemical stains and reactions. Additional muscle specimens were fixed in 10% neutral-buffered formalin, processed, embedded in paraffin, cut into 5 μm thick sections, stained with H&E, and examined by light microscopy.

The predominant histopathologic changes in the nerve specimens were marked, and in some fascicles variable, including nerve fiber loss, endoneurial fibrosis, and multifocal to diffuse mononuclear cell infiltrations (Fig 1). Nerve fiber loss was severe in the mandibular branch of the trigeminal nerve (Fig 1a) with variable severity among fascicles (Fig 1b). Fibrosis was identified by the Masson trichrome stain (Fig 1b). Nerve fiber loss also was marked in the glosopharyngeal (Fig 1c) and vagus (not shown) nerves, and variably severe in the oculomotor nerve with normal appearing fascicles adjacent to fascicles with marked nerve fiber loss (Figs 1d,e). Unmyelinated fibers were relatively spared (Fig 1f, oculomotor nerve). Longitudinal sections of the vagus nerve revealed marked perivascular infiltrates primarily consisting of lymphocytes and plasma cells, with fewer mononuclear cells and macrophages. Cross-sectional examination of the ganglia of the vagus nerve also revealed marked perivascular inflammation composed of lymphocytes and plasma cells along with central chromatolysis (Fig 2). Although the density of myelinated fibers was subjectively appropriate in the facial nerve and cellular infiltrates not observed, 10–15 fibers per fascicle showed active axonal degeneration (not shown). No abnormalities were found in the remaining nerves, including the optic, hypoglossal, and sciatic nerves. Moderate generalized myofiber atrophy without fiber type grouping was observed in the temporalis and masseter muscles (not shown). Cellular infiltrations were not observed in any of the muscle specimens. Based on the histopathologic findings, a diagnosis of a cranial polyneuritis and ganglionitis of unknown etiology was made.

Immunohistochemical staining of frozen sections of the trigeminal and glosopharyngeal nerves was performed using previously characterized monoclonal antibodies against canine leukocyte antigens including CD3 for T cells, CD4 for major histocompatibility complex (MHC) class II restricted cells, CD8 for MHC class I restricted cells, and CD11c for macrophage and dendritic cells (Fig 3). A monoclonal antibody against laminin was used to delineate Schwann cell basement membranes for morphologic context. Antibody localization was visualized by immunofluorescent staining with fluorescein isothiocyanate or rhodamine. The predominant cell type was CD11c+ macrophages and dendritic cells. Scattered CD3+ T lymphocytes also were evident with approximately equal numbers that were CD8+ or CD4+. These findings support an immune-mediated process with an unknown trigger.

To our knowledge, this is the first reported case of multisystem cranial polyneuritis and ganglionitis in any breed of dog. Golden Retrievers, however, are predisposed to several breed-specific neurologic disorders, including myopathic, neuropathic, and neuronopathic diseases, and many have been described. One of the most well-characterized neurological diseases of Golden Retrievers is muscular dystrophy. An inherited sensory ataxic neuropathy has been reported in 21 Swedish Golden Retrievers with onset at 2–8 months of age, as well as a sensory neuronopathy reported in 1 Golden Retriever.

In this case, clinical signs and pathologic changes were restricted to sensory, autonomic, and motor systems involving only cranial nerves without involvement of spinal nerves or roots. Although immunohistochemical staining of cellular infiltrates supported an immune-mediated process, specific triggers remain unclear. Infectious agents were not identified even with thorough histopathological studies; however, not all infectious agents can be identified histopathologically and additional infectious disease testing was not performed. Experimental autoimmune diseases have been studied in mouse models, including experimental autoimmune encephalomyelitis (EAE) and experimental autoimmune neuritis, which principally are mediated by CD4+ T-cells and macrophages. Dendritic cells (CD11c+) have been shown to play a role in the suppression of EAE. Immune-mediated diseases of the nervous system are commonly reported in veterinary medicine and have been thought to be related to previous antigenic stimulation from either a viral infection or other infectious etiology such as bacterial or protozoal. However, no etiologic agent has been identified in these autoimmune disease processes, or in the case presented here.
The earliest clinical signs in our dog were similar to those of a trigeminal neuropathy or neuritis. Trigeminal neuritis is most commonly associated with an inability to close the jaw. Other signs commonly noted with trigeminal neuritis include difficulty eating and drinking and hypersalivation. In addition to masticatory muscle atrophy, sensory and autonomic deficits also can be seen with trigeminal neuritis, such as the loss of facial sensation in the distribution of the trigeminal nerve and, less commonly, Horner’s Syndrome. Although our case did have sensory, motor, and autonomic deficits, the autonomic deficits supported a parasympathetic abnormality based on the fixed and dilated pupils, whereas Horner’s Syndrome is due to abnormal sympathetic function. A case of isolated sensory trigeminal neuropathy has been reported in 1 dog. Clinical signs included hypersalivation, coughing, dysphagia, and bilateral sensory loss over the distribution of the trigeminal nerve. However, motor function of the trigeminal nerve was preserved. Golden Retrievers also may be affected with masticatory muscle myositis; however, in this case, the clinical presentation differed and cellular infiltrates were not observed in the muscle specimens.

Sensory neuropathies may be inherited and breed associated, or can be acquired. Clinically, sensory neuropathies are slowly progressive and patients present with signs that can include sensory deficits, autonomic dysfunction, and other neurological symptoms.
with sensory signs consisting of pelvic limb ataxia and hypermetria, or dysmetria without paraparesis. Other clinical signs may include dysphagia, regurgitation, decreased to absent patellar reflexes, hyperesthesia, and self-mutilation. Because the motor nerve axons are intact, muscle atrophy is not a feature of this type of polyneuropathy. Clinical history and examination revealed decreased to absent patellar reflexes, hyperesthesia, and hypermetria, or dysmetria without paraparesis. Other physical examination findings reflect the severity of autonomic dysfunction. One unique clinical finding in our case was dysautonomia; the pathologic findings of the autonomic ganglia in cases of dysautonomia also indicate autonomic involvement, but is not pathognomonic. Dysfunction of the autonomic nervous system occurs in several diseases affecting multiple organ systems, including cardiovascular and nervous system disorders. Autonomic dysfunction, both of the parasympathetic and sympathetic nervous systems. Clinical history and physical examination findings reflect the severity of autonomic nervous system damage and can include dysuria with a distended bladder, mydriasis with absent PLR, dry mucous membranes, weight loss, decreased tear production, decreased nasal tone, vomiting or regurgitation, lethargy, elevated third eyelids, dysphagia, diarrhea, weakness, and abdominal pain. Megaeosphagus may be noted on thoracic radiographs. Although our case did show evidence of autonomic involvement (mydriasis OU, absent direct and consensual PLR OU, and megaeosphagus), there also was sensory and motor involvement, making an autonomic disorder as the primary cause of the dog’s clinical signs less likely. Pathologic findings of the autonomic ganglia in cases of dysautonomia also include neuronal degeneration with minimal inflammation, whereas our case displayed marked inflammatory changes in the ganglia and nerves. 

In summary, the clinical features of this case are indicative of a unique presentation with dysfunction of the sensory, autonomic, and motor components of several cranial nerves. Such a multisystem cranial neuropathy has not been reported previously, and based on the historical and immunohistochemical findings, an immune-mediated etiology for this cranial polyneuropathy and ganglionitis is suspected.

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References