Case Report

Resolution of diabetic neuropathy-associated tetraparesis and Horner's syndrome in a Labrador Retriever: a case report

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Abstract

This case report describes a 10-year-old neutered female Labrador with concurrent symptoms of weakness, ptosis, miosis, nictitating membrane prolapse, enophthalmos and diabetes mellitus. Insulin therapy initially improved the symptoms but failed to control hyperglycaemia. The dog was subsequently diagnosed with tetraparesis and Horner's syndrome due to diabetic neuropathy. Adjustments to insulin treatment improved glycaemic control but did not alleviate the neurological conditions. Gradual improvement was observed over three weeks, leading to complete resolution after five months. The neuropathic process involves glycation, oxidative stress and neural lesions.

Phenylephrine denervation hypersensitivity testing indicated a preganglionic lesion in the ocular sympathetic pathway. This case highlights the first diagnosis of diabetic neuropathy-related bilateral Horner's syndrome in a canine, expanding our understanding of clinical manifestations in diabetic neuropathy.

Keywords

Diabetic neuropathy; Tetraparesis; Horner's syndrome; Labrador Retriever; Canine diabetes mellitus; Glycation; Insulin therapy; Neural lesions; Ocular sympathetic pathway; Case report.

Abbreviations

BHS- bilateral Horner's syndrome
CDM - canine diabetes mellitus
OSP - ocular sympathetic pathway

Clinical condition and description of clinical presentation[1]

A 10-year-old neutered female Labrador presented with general weakness, bilateral ptosis (drooping eyelids), miosis (pupil constriction), nictitating membrane prolapse, and enophthalmos (sunken eyes), in addition to concomitant symptoms of canine diabetes mellitus (CDM). A urinalysis confirmed CDM and daily insulin therapy commenced. Although the concomitant symptoms partially improved after eight days, uncontrolled hyperglycaemia persisted. The dog was diagnosed with lower motor neuron tetraparesis (weakness of all limbs) and bilateral Horner's syndrome (BHS), both attributed to the same diabetic neuropathy. The patient's glycaemic control improved after adjusting the insulin treatment to twice daily. However, there was no improvement in tetraparesis or BHS. After three weeks, there was a partial improvement in the neuropathy and complete resolution of tetraparesis, and BHS resolved at five months. The tetraparesis and BHS were caused by neural lesions, indicating a neuropathic process of glycation and oxidation stress.[2]

Glycation is a process where blood glucose binds to proteins, lipids, or nucleic acids, occurring without enzymes. In CDM, glycation is triggered by hyperglycaemia resulting from reduced insulin dependency.[3] Excess glucose affects nerve tissue, impairing nerve cell function and structure.[4] Over time, this process forms advanced glycation end products, accumulating systemically and causing BHS autonomic neuropathy.[5]

Phenylephrine was used topically for denervation hypersensitivity testing, causing significant pupillary dilation after 30 minutes. This indicates a preganglionic location for the BHS-causing lesion to

the ocular sympathetic pathway.[6] BHS is a well-recognised diabetic neuropathy in humans.[7] Although commonly diagnosed in canines[8], this case marks the first published diagnosis of canine BHS as a clinical diabetic neuropathy.

Unlike humans, dogs lack anamnesis – the ability to describe symptoms verbally. Therefore, diagnosis relies on the observation of appearance or behaviour changes. Since dogs cannot verbally convey discomfort during physical examination, observing their posture and response to specific stimuli is crucial.[9] Moreover, testing, such as imaging or invasive procedures, may be less practical and feasible for dogs than humans.

Relevant anatomy and physiology

Sympathetic nervous system

The sympathetic nervous system in all mammals is responsible for the "fight or flight" response, mobilising the body's energy and resources in response to a threat.[10] The ocular sympathetic pathway (OSP) originates from the hypothalamus, descends through the brainstem, and emerges from the spinal cord at thoracic vertebrae T1-T3, synapsing at the cranial cervical ganglion.[11] The neurotransmitter acetylcholine is released by the fine terminal branches of the axon, binding to nicotinic cholinergic receptors at the postganglionic cell body.[12] From the cavernous sinus, post-ganglionic fibres run parallel to the ophthalmic division of the trigeminal nerve before synapsing at smooth muscle targets.[6] A lesion anywhere along the OSP can cause BHS.[13] In the case discussed, the lesion was localised to the preganglionic region. Such a localisation enables the potential for disruption of the sympathetic nervous system further along the pathway.

Canine diabetes mellitus may cause secondary bilateral Horner's syndrome in dogs and humans

Damage to the OSP by such underlying conditions as tumours, traumas, infections and neurological disorders can lead to symptoms of BHS. CDM can potentially result in diabetic neuropathy from nerve fibre degeneration and blood supply disruption to specific nerve structures such as the OSP.[15] Interruption of blood flow reduces nerve function, namely mitochondrial stress, leading to increased dysfunction.[16] Such damage in this neurological context is termed a lesion. This disruption interferes with the normal eye-related functioning of these nerves and may present as BHS.[17] Consequently, BHS could be a secondary consequence of diabetic neuropathy.[14] Importantly, CDM is not the primary causal factor behind BHS. Additionally, CDM showcases a spectrum of effects and uniquely impacts individuals. When diagnosing BHS as an indirect result of CDM, meticulous consideration of these two aspects is imperative.[18] BHS presents similarly in humans and dogs, encompassing three classic signs: miosis, ptosis and enophthalmos.[19] However, the fourth sign, anhydrosis (reduced sweating), can be challenging to identify in dogs.[11] Diagnosis in dogs necessitates special consideration due to differences in communication and examination techniques.

Autonomic neuropathic lesions

Prolonged uncontrolled CDM can damage neurons by glycation, a process whereby the accumulation of glucose end-product molecules leads to oxidative stress, inflammation and nerve damage.[20] Lesions can then form on nerves, disrupting function and causing diabetic neuropathy symptoms[2], including those observed in the above BHS case. Approximately fifteen post-ganglionic axons exit the cranial cervical ganglion for each preganglionic axon that enters, supplying the sympathetic nerve structures of the head and neck[21], demonstrating how a lesion located on a preganglionic nerve of the OSP produces the varied symptoms in the above BHS case.

Innervation of the eyelids and nictitating membrane

Ptosis and nictitating membrane prolapse occur in this case due to the lesion interrupting sympathetic innervation of smooth muscle associated with their respective functions. The drooping eyelid is a result of the inability of the superior tarsal muscle to contract appropriately[6], thereby narrowing the palpebral fissures.[22] Similarly, the smooth muscle usually responsible for holding the nictitating membrane in place becomes impaired, leading to prolapse.[23] The patient's apparent enophthalmos results from ptosis and nictitating membrane prolapse.[9] True enophthalmos is caused by a loss of volume in the orbit or function of extraocular muscles, unaffected by impaired sympathetic tone in this case.[24]

Innervation of the iris dilator muscle

The iris dilator smooth muscle plays a crucial role in regulating the amount of light that enters the eye. It is innervated by sympathetic nerves, which contract myoepithelial cells to temporarily dilate the pupil during the "fight or flight" response. However, due to the interruption of the sympathetic pathway via lesion damage, the iris muscle remains relaxed, and the parasympathetic tone is unopposed in activating the iris sphincter smooth muscle.[6] A lesion located on the preganglionic OSP would interrupt the innervation of the iris dilator muscle, which presents as miosis in this case.

Conclusion and treatment

Achieving control of the dog's glycaemic levels resolved the BHS symptoms. Maintaining glycaemic levels helps alleviate diabetic neuropathy symptoms by enhancing blood flow to vessels that supply the OSP, promoting nerve health and function. While a complete reversal of nerve damage may not be possible, a stable glycaemic environment can be conducive to nerve regeneration and repair. Continued control of glycaemic levels assists in minimising OSP dysfunction and supporting healthy mitochondrial function.[16]

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