

Narrowed Palpebral Fissure in a Dog

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Hansel, an 8-year-old neutered male German shepherd dog, was referred for persistent squinting and an inability to blink his right eye (OD).

History

Signs were present for 1 week. Hansel was otherwise normal, was current on vaccinations and heartworm and ectoparasite preventives, and had no pertinent medical history (eg, exposure to toxins, history of trauma). No blepharospasm was reported by the owner.

Examination

Physical examination revealed deviation of the nasal planum to the right and slight elevation of the right ear (**Figure 1**). Ophthalmoscopic examination was normal. Neurologic examination included evaluation of mentation, gait, postural reactions, spinal reflexes, tone, and muscle mass in all limbs; all were within normal limits. Evaluation of the cranial nerves revealed that the palpebral reflex and menace response were absent OD. A narrowed palpebral fissure OD was noted. Response to stimulation of the nasal mucosa was normal. All other cranial nerve reflexes were normal.

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Diagnostics

CBC, serum chemistry panel, thoracic radiographs, and thyroid hormone testing (thyrotropin and free thyroxine by equilibrium dialysis) were normal. MRI of the head was normal.

Diagnostic Considerations

Anatomic diagnosis: Facial nucleus in the medulla or the facial nerve (cranial nerve VII) or hemifacial tetanus (HT) of the muscles of facial expression, including the obicularis oculi muscle (narrowed palpebral fissure) and levator nasolabialis (deviated nasal planum), or denervation atrophy (contracture) of the facial muscles. The lack of other neurologic deficits suggests the lesion did not involve the medulla.

Differential diagnoses: From the medulla, the facial nerve exits the cranial cavity via the internal acoustic meatus to enter the facial canal within the petrosal portion of the temporal bone. The facial nerve exits the facial canal via the stylomastoid foramen. Once extracranial, the facial nerve courses rostrally just ventral to the external ear canal where it branches. Causes to consider include disease of the middle ear, (eg, otitis media, which secondarily affects the facial nerve), or primary diseases of the facial nerve. Primary diseases include inflammation, neoplasia, aberrant blood vessel compressing the facial nerve, and trauma.



- ▲ At presentation, the palpebral fissure is narrowed on the right (**arrow**) as compared with the left. The nasal planum is deviated to the right (**arrowhead**). The right ear is positioned slightly more caudal on the head as compared with the left ear.

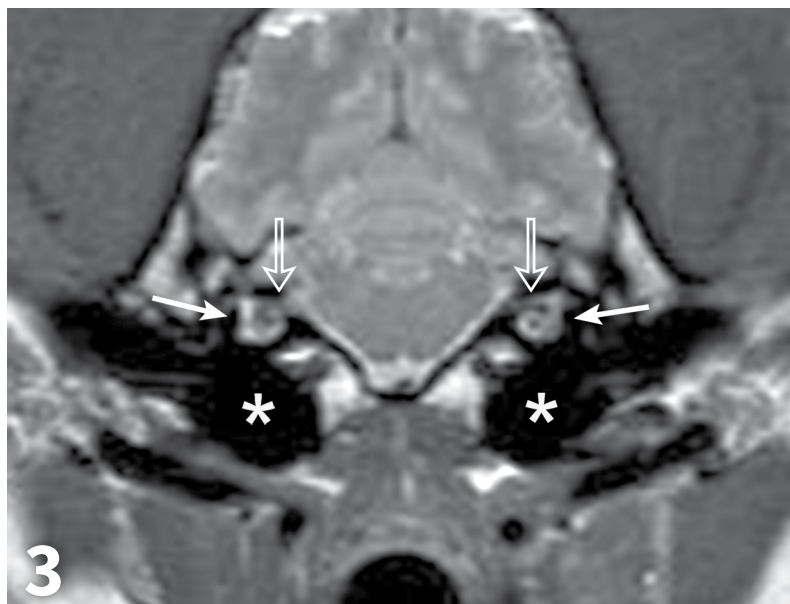
ASK YOURSELF

- ▶ What is the difference between ptosis and a narrowed palpebral fissure?
- ▶ What are the muscles and nerves that may cause a narrowed palpebral fissure?
- ▶ What is an appropriate differential list and diagnostic plan for a narrowed palpebral fissure?

CBC = complete blood count
HT = hemifacial tetanus
MRI = magnetic resonance imaging
OD = oculus dexter (ie, right eye)



▲ On anesthetic induction for MRI, deviation of the nasal planum was not present (**arrowhead**). The dog's closed eyelids make it difficult to appreciate the narrowed palpebral fissure. Note the near-symmetrical position of the ears.



▲ A transverse plane, proton density MRI at the level of the medulla and rostral cerebellum of the patient. The normal facial and vestibulocochlear nerves are seen exiting the internal acoustic meatus (**open arrows**). Normal cochlea are seen bilaterally (**solid arrows**). The normal tympanic cavities are filled with air (**asterisks**).

In humans, HT is associated with microvascular compression of the facial nerve by aberrant vasculature.

Diagnosis

Canine idiopathic HT

Discussion

During general anesthesia for the MRI, the patient's narrowed palpebral fissure, deviation of the nasal planum, and abnormal ear position resolved (**Figures 2 and 3**). On recovery from anesthesia, the abnormalities returned. This confirmed HT^{1,2} and excludes from consideration denervation atrophy (contracture), as relaxation of the muscles under anesthesia would not occur.

HT results in persistent contraction of the facial muscles innervated by the facial nerve. A narrowed palpebral fissure, deviation of the nasal planum

toward the affected side, and a caudal position of the ear are seen. Under general anesthesia or with local anesthesia of the facial nerve, muscle activity is inhibited, muscle relaxation ensues, and the patient appears normal.¹ In some cases, ipsilateral, hemifacial paralysis, which then resolves, may precede HT. Used synonymously, *hemifacial spasm* is a misnomer because muscle spasms are not present.

In humans, HT is associated with microvascular compression of the facial nerve by aberrant vasculature. Treatment options (eg, botulinum toxin injections into the affected muscles, surgical microvascular decompression) exist.³ HT has been reported in 2 dogs secondary to a

HT = hemifacial tetanus

brain lesion.⁴ In the authors' experience, HT in dogs mostly occurs secondary to an irritative lesion of the facial nerve. Irritative lesions likely cause excessive activity (depolarization) of the nerve rather than a lack of function.¹

Diagnostics are aimed at identifying a metabolic disorder or structural lesion of the nerve or its nucleus in the medulla. An otoscopic examination should be performed to evaluate for abnor-

malities in the external ear canal because the facial nerve runs just ventral to it. A diagnostic evaluation consisting of CBC, serum chemistry panel, urinalysis, and thyroid hormone testing should help identify metabolic causes associated with nerve dysfunction. Finally, MRI of the head is used to evaluate the medulla and the course of the facial nerve. If an underlying cause is not identified, HT is assumed secondary to an irritative lesion. In such cases,

supportive treatment aimed at muscle relaxation or empiric therapy for otitis media is not necessary.

Treatment

Given the normal results of the diagnostic testing and presumptive diagnosis, treatment was not pursued.⁴ Although the underlying cause is still not fully understood, it appears to remain a benign condition. Owners should be warned that the signs can remain indefinitely.

DID YOU ANSWER?

- ▶ Ptosis is the drooping or sagging of a body part, which here refers to a drooping superior eyelid.⁵ A narrowed palpebral fissure can result from ptosis, but it may also result from continual contraction of the muscles of the eyelids, blepharospasm, or enophthalmos.¹
- ▶ The orbitalis muscle is responsible for elevating the superior eyelid and is innervated by sympathetic axons.⁵ Denervation of this muscle leads to ptosis and, subsequently, a narrowed palpebral fissure. Other signs of Horner syndrome—miosis, a protruding third eyelid, and enophthalmos—will also be present.^{1,6}

In addition to the orbitalis muscle, the levator palpebrae superioris muscle is responsible for elevating the superior eyelid. This muscle is innervated by the oculomotor nerve (cranial nerve 3).

The levator palpebrae superioris muscle, innervated by the oculomotor nerve (cranial nerve III), elevates the superior eyelid. Denervation of this muscle leads to ptosis.⁵ Because the

oculomotor nerve innervates multiple extraocular muscles and the iris sphincter muscle, lesions of the oculomotor nerve also result in a ventrolateral strabismus and a dilated pupil.¹

The orbicularis oculi muscle, innervated by the facial nerve, closes the palpebral fissure. Because of its small size in dogs, denervation rarely causes ptosis. However, denervation atrophy (contracture) of the orbicularis oculi muscle narrows the palpebral fissure. Likewise, continual contraction is observed with HT from an irritative lesion of the facial nerve.¹ Alternatively, tetanus of the facial muscle may be part of generalized tetanus secondary to the toxin elaborated by *Clostridium tetani*.

The levator anguli oculomotor medial, which is innervated by the facial nerve (cranial nerve 7), is the third muscle that plays a significant role in elevating the superior eyelid. This muscle plays a greater role in cats than dogs. Consequently, ptosis of the

superior eyelid can be observed in cats with facial paralysis.

The muscles of mastication provide medial support of the eye in the orbit. Atrophy of the muscles of mastication results in enophthalmos. A narrowed palpebral fissure results from the caudal position of the eye in the orbit.

- ▶ A thorough neurologic examination should *always* be performed; identifying neurologic deficits aside from a narrowed palpebral fissure will determine the anatomic diagnosis. From this, a list of appropriate differential diagnoses can be developed:
 - Ptosis: Horner syndrome, oculomotor nerve denervation, facial nerve denervation (rare)
 - Facial muscle contraction: HT
 - Other: Denervation atrophy (contracture) of the facial muscles or masticatory muscle atrophy

Ancillary procedures will be dictated based on the observation of ptosis, HT, denervation atrophy (contracture), or masticatory muscle atrophy. ■

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NexGard® (afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:

NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl].

Indications:

NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of Black-legged tick (*Ixodes scapularis*), American Dog tick (*Dermacentor variabilis*), Lone Star tick (*Amblyomma americanum*), and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month.

Dosage and Administration:

NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

NexGard can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:

Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:

Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:

There are no known contraindications for the use of NexGard.

Warnings:

Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Precautions:

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

Adverse Reactions:

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N ¹	% (n=415)	N ²	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

¹Number of dogs in the afoxolaner treatment group with the identified abnormality.

²Number of dogs in the control group with the identified abnormality.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard and experienced no seizures throughout the study.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

Mode of Action:

Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:

In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was > 93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*. 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days.

Animal Safety:

In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, antelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:

Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:

NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

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