Journal of Veterinary Internal Medicine
Open Access

Case Report
J Vet Intern Med 2015;29:1117–1121

Bilateral Trochlear Nerve Palsy as a Consequence of Cerebellar Medulloblastoma: Clinical and Pathological Findings in a Calf

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Key words: Dorsomedial ocular rotation; Neurological diseases; Bovine; Central nervous system.

A 1-month old female Holstein calf had not been able to stand since birth. Delivery was uncomplicated and no treatment had been administered before admission.

On physical examination, the calf had slightly decreased body condition, but was bright and alert. The calf was in lateral recumbency with spastic extension of all four limbs and opisthotonus. If positioned in left lateral recumbency, the calf raised its head, which fell immediately to the ground after rotation of the neck. The calf made no attempt to raise its head when lying in right lateral recumbency. Attempts to passively position the calf in a quadrupedal stance or in sternal recumbency were unsuccessful. Despite the lateral recumbency, the calf was able to suckle.

A thorough neurologic examination was carried out. Mental status and consciousness were considered normal. Because of recumbency, postural reactions could not be tested. The menace response was absent in the right eye and present in the left eye. In both eyes, the medial end of the pupil was rotated dorsally. This dorsomedial rotation of the eyes was not affected by changes in the position of the head. Moreover, incomitant strabismus (i.e., degree of misalignment of the eyes varying with the position of the head) was evident, particularly in left lateral recumbency, characterized by an upward deviation of the visual axis of the left eye (hypertropia) and inward deviation of the visual axis of the right eye (esotropia, Fig. 1). Other routine tests for evaluation of the cranial nerves were normal as were the spinal reflexes. Mild neutrophilic leukocytosis was present on the CBC.

Abbreviations:

CNS	central nervous system
CN	cranial nerve
CSF	cerebral spinal fluid
H&E	hematoxylin and eosin
CK	cytokeratin AE1/AE3
Vim	vimentin
NSE	neuron-specific enolase
Syn	synaptophysin
GFAP	glial fibrillary acidic protein
NFP	neurofilament protein

On the basis of the clinical and neurologic findings, the tentative anatomical diagnosis was a congenital lesion, located at the level of the right side of the cerebellum with bilateral involvement of the trochlear nerve (cranial nerve [CN] IV) and possibly, but less likely, of the other nerves innervating the extraocular muscles (oculomotor nerve, CN III and abducent nerve, CN VI).

The most likely differential diagnoses were malformations (e.g., dermoid cyst in the caudal fossa compressing the cerebellum) and embryonal tumors (e.g., medulloblastomas directly or indirectly involving the cerebellum). Bacterial meningoencephalitis, mainly affecting the caudal fossa, also was considered but excluded by the results of cerebrospinal fluid (CSF) evaluation. Lumbosacral CSF samples were analyzed and showed albuminocytologic dissociation, the total proteins being 113 mg/dL (reference range, <30 mg/dL) and the total nucleated cell count 9 cells/μl (reference range, <10 cells/μL). Because of the poor prognosis, the calf

Fig 1. Calf affected by incomitant strabismus. Note the upward deviation of the visual axis of the left eye (hypertropia) and the inward deviation of the visual axis of the right eye (esotropia).

This article was published online on 25 June 2015. An error was subsequently identified, hence it was corrected and re-posted on 16 July 2015.

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Submitted February 17, 2015; Revised April 15, 2015; Accepted May 11, 2015.

DOI: 10.1111/jvim.13568

was euthanized, and postmortem examination was carried out.

Gross examination identified the presence of a unilateral, soft, grayish-to reddish- infiltrating mass approximately 10 cm in length at the level of the right cerebellar hemisphere, compressing the right occipital lobe rostrally and the dorsal part of the brainstem including the fourth ventricle and the rostral medullary velum ventrally (Fig. 2). Sectioning disclosed that the tumor extended to the midbrain but did not invade the third ventricle. The tumor was covered by the pia mater. The effect of tumor-related compression on the surrounding structures was confirmed by deformation of brainstem structures. Table 1 presents the measurements of the thickness of the medulla oblongata, pons and mesencephalon as compared to those of a control calf of the same age and breed euthanized for a non-neurologic condition. No other pathological findings were found in other organs.

Tissues samples of the mass were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 4 μm, and stained with hematoxylin and eosin (H&E) for histopathologic examination. Microscopic examination of the cerebellar mass disclosed a neoplasm composed of a fairly uniform and closely packed round to polygonal cell population, often arranged in densely packed sheets or bands. Many neoplastic cells similar to those of the granular layer of the cerebellar cortex extended into the leptomeninges. Palisading of the cells, and complete or incomplete Homer Wright rosette formation were observed frequently (Fig. 3). There were 2–3 mitotic figures per high power field (400×). Neoplastic cells, characterized by scant cytoplasm and round to elongated hyperchromatic nuclei, caused by the abundant coarsely distributed chromatin, were interpreted as undifferentiated cells expressing proteins specific to neurons and glia. The nuclei contained ≥1 nucleoli. For the most part, a scanty fibrovascular stroma was present in the tumor. Hemorrhagic foci also were present. The final histopathologic diagnosis was cerebellar medulloblastoma.

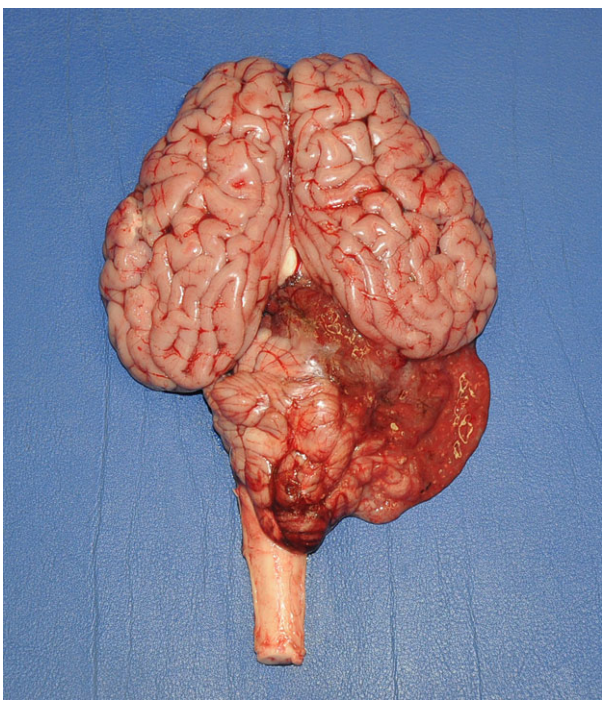

Fig 2. Anatomic image of the dorsal view of the brain and cerebellum. Note the mass in the right cerebellar hemisphere, between the dorsal part of the brainstem and the right occipital lobe.

Table 1. Thickness of brainstem structures in the affected calf and in a control calf

	Affected calf (cm)	Control calf (cm)
Medulla oblungata	0.50	0.90
Pons	0.65	1.10
Mesencephalon	1.20	1.75

To better define the characteristics of the medulloblastoma, unstained paraffin-embedded sections were processed using the streptavidin-biotin peroxidase technique and immunohistochemical evaluation of cytokeratin[a] (CK AE1/AE3, dilution 1 : 150), vimentin[a] (VIM, dilution 1 : 100), S-100 protein[a] (dilution 1 : 1600), neuron-specific enolase[a] (NSE, dilution 1 : 1200), synaptophysin[a] (Syn; dilution 1 : 20), glial fibrillary acidic protein[a] (GFAP, dilution 1 : 8000) and neurofilament protein[a] (NFP, dilution 1 : 200).

The following were the immunohistochemical findings: CK AE1/AE3 was completely negative, whereas immunoreactivity for VIM was intense and diffuse. The neoplastic cells were focally positive for S-100, diffusely positive for NSE and slightly positive for Syn (Fig. 4). Rare pale-staining islands of GFAP-positive cells were interspersed between the predominant medulloblastoma cells.

These findings supported the neuronal origin of the tumor cells, confirming the morphological diagnosis of cerebellar medulloblastoma.

Pan-CK-negative immunoreactivity permitted the exclusion of a metastatic small cell undifferentiated carcinoma, whereas vimentin immunoreactivity permitted characterizing the mesenchymal cells of the tumors. The specific neuronal markers (S-100 protein, NSE, Syn, GFAP and NFP) demonstrated the neuroectodermal origin of the mass. They showed variable reactivity, depending upon the degree of tumor differentiation.

Focally positive staining for S-100, diffuse positive staining for NSE and slightly diffuse positive staining for Syn were more consistent than GFAP and NFP. The GFAP reactivity was explained by the presence of astrocytic components which could be found in pale-staining islands within the tumor.

To better evaluate the involvement of the nuclei of the cranial nerves innervating the extraocular muscles (CN III, CN IV, CN VI), paraffin-embedded sections of the thickened brainstem were stained with thionin. The same study was carried out in the control calf.

The topography and cytoarchitectonic features of the three nuclei did not differ from those of the normal calf examined.

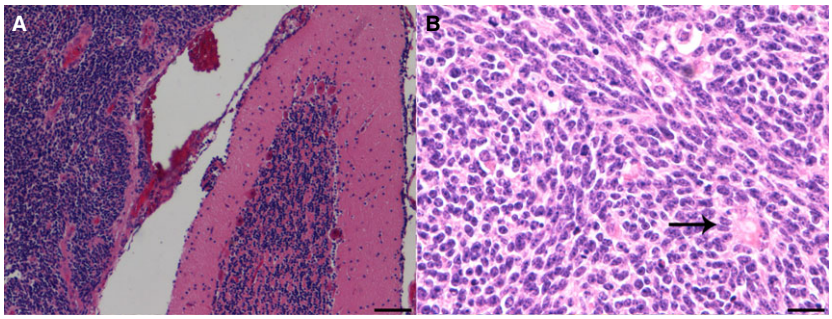

Fig 3. (**A** and **B**) Histological images of the cerebellar medulloblastoma. (A). Medulloblastoma (on the left) and cerebellar tissue (on the right). The majority of the neoplastic cells are similar to those of the granular layer of the cerebellar cortex. H&E. Bar = 100 μm. (B) Medulloblastoma composed of a fairly uniform and closely packed round to polygonal cell population, often arranged in densely packed sheets or bands, with scant cytoplasm and round to elongated hyperchromatic nuclei containing one or more evident nucleoli. An incomplete Homer Wright rosette is visible (arrow). Note the presence of a scanty fibrovascular stroma. H&E. Bar = 25 μm.

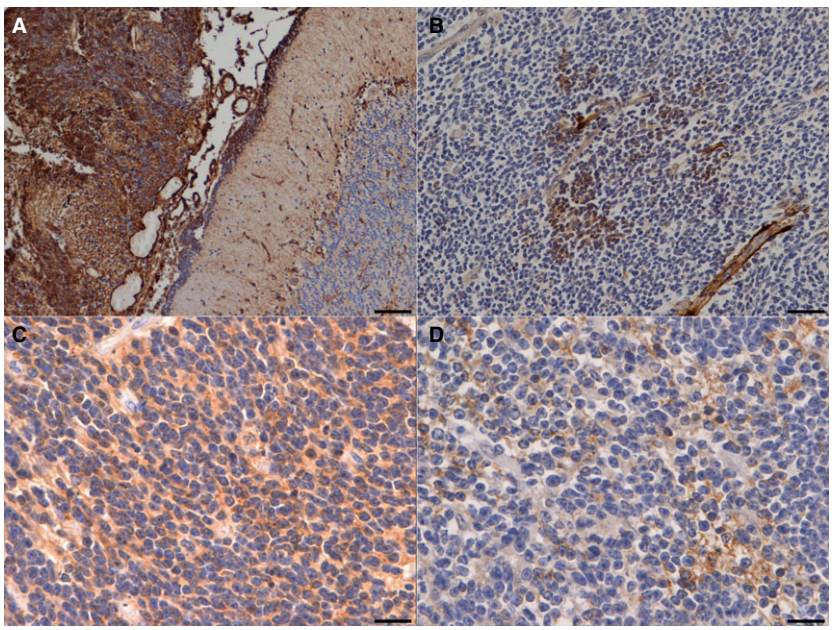

Fig 4. (**A–D**) Immunohistochemical images of the medulloblastoma. (A) Neoplastic cells (on the left) have intense, diffuse cytoplasmic immunohistochemical expression of vimentin, compared with different cellular immunoreactivity of the cerebellar layers (on the right). Hematoxylin counterstain. Bar = 100 μm. (B) Immunohistochemical expression focally positive for S-100. Hematoxylin counterstain. Bar = 50 μm. (C and D) Immunohistochemical expression diffuse for NSE and slightly positive for Syn. Hematoxylin counterstain. Bar = 25 μm.

In both animals, the motor nucleus of the oculomotor nerve (*nucleus motorius n. oculomotorii*), located in the tegmentum of the midbrain at the level of the rostral colliculus and ventral to the periacqueductal gray matter, contained irregularly oriented neurons with multipolar morphology. These cells infiltrated the fibers of the medial longitudinal fasciculus, especially in the caudal part of the nucleus. The motor nucleus of the abducent nerve (*nucleus motorius n. abducentis*), an ovoid structure located in the dorsomedial portion of the midpontine tegmentum, was characterized by small multipolar neurons containing small Nissl granules. The motor nucleus of the trochlear nerve (*nucleus motorius n. trochlearis*), located in the tegmentum of the midbrain at the level of the caudal colliculus, contained irregularly distributed neurons with a multipolar morphology.

We describe a case of cerebellar medulloblastoma, a rare tumor belonging to the family of central primitive neuroectodermal tumors,[1–3] a differential diagnosis that must be included in calves with cerebellar syndrome, especially when occurring from birth or in young animals. In human medicine, medulloblastoma constitutes up to 25% of central nervous system (CNS) tumors in children, being the most common malignant tumor of the cerebellum.[4] In veterinary medicine, medulloblastoma has been reported in dogs, cats, pigs and other species, such as rats, mice, nonhuman primates,[2,5–9] and occasionally in cattle.[10,11,12,13,14,15]

The unusual feature of our case was the presence of bilateral trochlear nerve palsy caused not by an intrinsic lesion of the trochlear nuclei, but by compression of the nerves at the level of their decussation. Expansion of

the tumor compressed the rostral medullary velum and the thin, transparent lamina of white matter which rostrally delimits the fourth ventricle and contains the decussation of CN IV.

The presence of a cerebellar lesion was suspected clinically on the basis of opisthotonus and hyperextension of the forelimbs. These findings constitute "decerebellate posture",[16] and are attributed to defective inhibitory action of the rostral lobe of the cerebellum on the stretch reflex mechanism of the antigravity muscles. Decerebellate posture usually is accompanied by flexion of the hips because of hypertonia of the hypaxial muscles which flex the hips. Extension of the pelvic limbs was attributed specifically to the involvement of the ventral lobules of the rostral lobe.[16]

Although not conclusive for the diagnosis, unilateral absence of the menace response in the presence of normal pupillary size and reactions to light and conserved facial nerve function, was considered consistent with an extensive lesion of the ipsilateral cerebellum, possibly involving the lateral and the interposital nuclei.[16] In addition, the wide swinging excursions of the neck were considered consistent with a cerebellar disorder.[17]

The presence of trochlear nerve dysfunction was clinically diagnosed on the basis of the bilateral dorsomedial rotation (extorsion) of the eyes. The fourth cranial nerve, by innervating the dorsal oblique muscle of the contralateral eye, induces rotation of the dorsal portion of the globe nasally (intorsion) and, depending on the direction of the gaze and the position of the head, lowers and abducts the globe.[18] The fact that the dorsomedial rotation of the eyes was not influenced by changes in the position of the head was additional evidence of the involvement of CN IV.

Clinical evaluation of the alignment and movement of the eyes permitted us to conclude that involvement of CN III and CN VI was unlikely. In fact, dysfunction of CN III would have provoked ventrolateral strabismus and inability to rotate the eye dorsally, ventrally or medially during oculovestibular testing (external ophthalmoplegia) and possibly a dilated unresponsive pupil (internal ophthalmoplegia). Dysfunction of CN VI also would have caused medial strabismus, inability of the eye to cross the midline during horizontal oculovestibular testing, and inability to retract the eye during corneal reflex testing. Of the above-mentioned findings potentially linked to CN III and CN VI dysfunction, medial strabismus of the right eye was the only finding.

Based on similarities in human medicine, incomitant strabismus (hypertropia of the left eye and esotropia of the right eye) was also considered consistent with CN IV palsy and was attributed to impaired ventral movement and abduction of the dorsal oblique muscles.[19] However, incomitant strabismus also might have been attributed to cerebellar dysfunction, as evidenced by the abnormalities in ocular alignment reported in humans and laboratory animals with discrete lesions in the cerebellum alone.[20,21]

In humans, acquired bilateral CN IV palsy is considered a definite sign of a single lesion in the region of the decussation of the trochlear nerves, and is also referred to as superior medullary velum syndrome.[22] This syndrome has been reported mainly with trauma and occasionally with vascular, neoplastic and inflammatory disorders.[19,22–24]

True CN IV palsy in animals is very rare.

In the literature, cases of dorsomedial rotation of the eye are reported in thiamine-responsive polioencephalomalacia as a consequence of dysfunction of the motor nucleus of CN IV.[25] Lead and water intoxication as well as bacterial meningitis are other conditions that can be associated with dorsomedial rotation of the eyes. In these situations, dorsomedial rotation is attributed to severe forebrain lesions involving the upper motor pathways that regulate eye position.[26]

The dorsomedial ocular rotation reported in a case of congenital cerebellar hypoplasia and cerebellar abiotrophy was attributed to abnormalities in vestibulocerebellar tonic control of the extraocular muscles.[26]

In conclusion, bilateral trochlear nerve palsy in neonatal calves should be considered as a finding that prompts suspicion of a congenital space-occupying mass compressing the decussation of CN IV located at the level of the rostral medullary velum. In our case, the presence of decerebellate posture helped localize the primary lesion but, a mass also could have been included in the differential diagnosis based solely on the CN IV palsy.

Footnote

[a] Dako, Glostrup, DK.

Acknowledgments

Conflict of Interest Declaration: Authors disclose no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

References

1. Giangaspero F, Bigner SH, Kleihues P, et al. Medulloblastoma. In: Kleihues P, Cavenne WK, eds. Pathology and Genetics of Tumours of the Nervous System. Lyon, France: International Agency for Research on Cancer; 2000:129–137.

2. Koester A, Higgins RJ. Tumors of the nervous system. In: Meuten DJ, ed. Tumors in Domestic Animals, 4th ed. Ames, IA: Iowa State press; 2002:697–738.

3. Maxie MG, Youssef S. Nervous system. In: Maxie MG, ed. Jubb, Kennedy, and Palmer's Pathology of Domestic Animals, Vol. 1, 5th ed. Oxford: Elsevier; 2007:281–457.

4. Huppmann AR, Orenstein JM, Jones RV. Cerebellar medulloblastoma in the elderly. Ann Diagn Pathol 2009;13:55–59.

5. Berthe J, Barneon G, Richer G, et al. A medulloblastoma in a baboon (*Papio papio*). Lab Anim Sci 1980;30:703–705.

6. Krinkle GJ, Kaufmann W, Mahrous AT, et al. Morphologic characterization of spontaneous nervous system tumors in mice and rats. Toxicol Pathol 2000;48:178–192.

7. Kuwambara M, Kitagawa M, Sato T, et al. Early diagnosis of feline medulloblastoma in the vermis. Vet Rec 2002;150:488–489.

8. Mandrioli L, Biserni R, Panarese S, et al. Immunohistochemical profiling and telomerase activity of a canine medulloblastoma. Vet Pathol 2011;48:814–816.

9. Mukaratirwa S, Rogersdon P, Blanco AL, et al. Spontaneous cerebellar primitive neuroectodermal tumor in a juvenile cynomolgus monkey (*Macaca Fascicularis*). Toxicol Pathol 2012;40:951–954.

10. Cordy DR. Medulloblastoma in a steer. Cornell Vet 1953;43:189–193.

11. McGavin MD. A medulloblastoma in a calf. Austral Vet J 1961;37:390–393.

12. Jolly RD, Alley MR. Medulloblastoma in calves: a report of three cases. Pathol Vet 1969;6:463–468.

13. Fankhauser R, Fatzer R, Hermann M. Medulloblastomas in bovine twins of different sexes. Schweiz Arch Tierheilkd 1982;124:363–367.

14. Scarratt WK, Gamble DA. Cerebellar medulloblastoma in a calf. Compend Contin Educ Pract Vet 1983;5:S627–S630.

15. Guarda F, Biolatti B. Cerebellar medulloblastoma in two calves. Summa 1987;4:33–35.

16. De Lahunta A, Glass E. (Eds) Upper motor neuron. In: Veterinary Neuroanatomy and Clinical Neurology, 3rd ed. St. Louis, MO: Saunders Elsevier; 2009:192–220.

17. Mayhew IG. Incoordination of the Head and Limbs: Cerebellar Diseases. In: Mayhew IG, editor. Large Animal Neurology, 2nd ed. Chichester: Wiley-Blackwell; 2009:143–146.

18. Scagliotti RH. Comparative neuro-ophthalmology. In: Gelatt KN, ed. Veterinary Ophthalmology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999:1307–1400.

19. Prasad S, Volpe NJ. Paralytic strabismus: third, fourth and sixth nerve palsy. Neurol Clin 2010;28:803–833.

20. Versino M, Hurko O, Zee DS. Disorder of binocular control of eye movements in patients with cerebellar dysfunction. Brain 1996;119:1933–1950.

21. Wong AMF. Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy. J AAPOS 2010;14:61–67.

22. Barr DB, McFadzean RM, Hadley D, et al. Acquired bilateral superior oblique palsy: a localising sign in the dorsal midbrain. Eur J Ophthalmol 1997;7:271–276.

23. Sadun F, De Negri AM, Santopadre P, et al. Bilateral trochlear nerve palsy associated with cryptococcal meningitis in human immunodeficiency virus infection. J Neuroophthalmol 1999;19:118–119.

24. Simon S, Sandhu A, Selva D, et al. Bilateral trochlear nerve palsies following dorsal midbrain haemorrhage. N Z Med J 2009;122:72–75.

25. De Lahunta A, Glass E. (Eds) Lower motor neuron: general somatic efferent, cranial nerve. In: Veterinary Neuroanatomy and Clinical Neurology, 3rd ed. St. Louis, MO: Saunders Elsevier; 2009:134–167.

26. Mayhew IG. Strabismus. In: Mayhew IG, editor. Large Animal Neurology, 2nd ed. Chichester: Wiley-Blackwell; 2009:101–103.