

Intracranial oligodendroglioma with optic nerve infiltration in a Labrador retriever

Intracraniaal oligodendroglioma met uitbreiding naar de nervus opticus bij een labrador retriever

¹R. Jeurings, ¹K. Van Driessche, ¹L. Bosseler, ¹C. de Vries, ²A. Vanhaesebrouck, ³I. Gielen, ⁴A. Oevermann, ¹K. Chiers

¹Department of Pathology, Bacteriology and Poultry Diseases,

²Department of Small Animal Medicine and Clinical Biology,

³Department of Medical Imaging and Small Animal Orthopedics, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

⁴Neurocenter, Experimentelle Klinische Forschung, DCR-VPH, Vetsuisse Fakultät Bern, Bremgartenstrasse 109a, Postfach 8466, CH-3001 Bern, Switzerland

rianejeuring@hotmail.com

ABSTRACT

A seven-year-old neutered male Labrador retriever was presented with behavioral changes and reduced vision. Neurological examination revealed blindness of the left eye with a positive pupillary light reflex and a decreased mental status. Blood and cerebrospinal fluid analyses showed no abnormalities. MRI revealed a deviant area located in the thalamic, hypothalamic and caudate nuclear regions. Invasion of the left optic nerve was also observed. The dog was euthanized after 38 days of palliative treatment. Necropsy showed a non-encapsulated extruding white lardaceous mass, with a diameter of 2 cm, in the white matter, located in the ventral thalamic region near the chiasma opticum, which extended along the left optic nerve. Histologically, neoplastic cells had a “fried egg” appearance. Immunolabelling for glial fibrillary acidic protein demonstrated the presence of numerous reactive astrocytes. The tumor was diagnosed as a low grade (II) intracranial oligodendroglioma with infiltration of the optic nerve.

SAMENVATTING

Een gecastreerde labrador retriever van zeven jaar oud werd aangeboden met klachten van abnormaal gedrag en een verminderd zicht. Op neurologisch onderzoek werd blindheid van het linkeroog gediagnosticeerd samen met een abnormaal bewustzijn. Bloedonderzoek en onderzoek van het cerebrospinaal vocht toonden geen afwijkende waarden. Op MRI werd een massa gelokaliseerd ter hoogte van de thalamus, de hypothalamus en de nucleus caudatus. Ook de linkernervus opticus leek betrokken in dit proces. Na een palliatieve behandeling gedurende 38 dagen werd de hond geëuthanaseerd en er werd een autopsie uitgevoerd. Hierbij werd een witte, zachte, uitpuilende, niet-omkapselde massa van 2 cm waargenomen. Deze massa was gelokaliseerd in de witte stof van de ventrale thalamusregio, dicht bij het chiasma opticum, en strekte zich uit langs de linkernervus opticus. Op histologisch onderzoek hadden de neoplastische cellen het uitzicht van “spiegeleieren”. Tussen deze cellen werden veel reactieve astrocyten waargenomen bij immunohistochemie. Het gezwell werd gediagnosticeerd als een astrocytenrijk oligodendroglioma graad II met invasieve groei in de linkernervus opticus.

INTRODUCTION

Neoplasia of the nervous system is a relatively frequent finding in dogs. There are reports of incidence rates varying from 0.145 to 3 % (Snyder *et al.*, 2006). Over 70 % of the primary brain tumors occur in dogs over six years of age, while only 10 % occur in dogs of three years of age or younger (Koestner and Higgins, 2002). Overall, neoplasia of the nervous system has been reported in 1 to 3 % of the dogs in which an au-

topsy is performed (Braund *et al.*, 2005). Breed and sex predilections have not been reported.

Primary central nervous system tumors may originate from neuroectodermal, ectodermal and/or mesodermal cells. These tumors rarely metastasize via cerebrospinal fluid or hematogenous route, but can sometimes invade the surrounding tissues. Secondary tumors may originate from a hematogenous metastasis of a different site of the body or from infiltrating neoplasms of the surrounding tissues (Braund *et al.*, 2005).

The most common primary brain tumors in dogs are meningiomas, followed by astrocytomas and oligodendrogliomas. Undifferentiated sarcomas, choroid plexus tumors, medulloblastomas and ependymomas are less frequently observed (Snyder et al., 2006).

Oligodendrogliomas are neoplasms originating from oligodendrocytes, which play an important role in the maintenance of the axonal myelin sheaths. In dogs, this type of tumor has been reported to comprise up to 14 % of the primary brain tumors (Snyder, 2006). Most often, these tumors occur in dogs of median age (Bullard et al., 1987). They are generally located in the white or gray matter of the cerebral hemispheres, and are usually well-demarcated, gelatinous and soft tumors, with multifocal hemorrhages (Koestner and Higgins, 2002).

Based on the most frequent localization of the tumor, which is at the cerebral hemispheres, patients are expected to show symptoms typically associated with supratentorial disorders, such as proprioceptive deficits, abnormal mental status or behavior, impaired vision and epileptic seizures (Kraft and Gavin, 1999; LeCouteur, 1999). Different symptoms may occur due to secondary changes in the brain or a different localization of the tumor (Braund et al., 2005).

Central nervous tumors have generally been classified by the World Health Organization (WHO) into four different grades. This classification includes a grading scheme that is a 'malignancy scale' ranging across a wide variety of neoplasms rather than a strict histological grading system whereby grade IV possesses the most malignant features. According to this system, oligodendrogliomas are divided into two groups: grade II (benign) and grade III (anaplastic, malignant) oligodendrogliomas (Louis et al., 2007). Oligodendrogliomas rarely metastasize and only a few reports describe multiple oligodendrogliomas in dogs (Koch et al., 2011).

The best way to visualize brain tumors is by using computed tomography (CT) or, even better, magnetic resonance imaging (MRI) (Kraft and Gavin, 1999). Unfortunately, medical imaging cannot differentiate oligodendrogliomas from other tumors (Young et al., 2010). Therefore, the definitive diagnosis is still based on histological examination (Braund et al., 2005).

CASE REPORT

Case history

A seven-year-old neutered male Labrador retriever was presented with three main complaints. During the last six months, behavioral changes and periuria (urinating randomly in the house) were noticed by the owner. The dog alternately gave no response or showed aggressive and hostile behavior as a reaction to the owners calls. On top of this, reduced vision had started to become obvious in the last four weeks as the dog had begun running into objects.

Clinical examination revealed a decreased mental status and a body temperature of 37,9 °C. On neuro-

logical examination, blindness of the left eye was observed as both the menace response and reaction to the cotton ball test were absent. The pupillary light reflex appeared to be present in both eyes. These results could have been explained by central blindness with a lesion in the right visual cortex, but to confirm this diagnosis further examination by the use of medical imaging was required.

Since abnormal behavior, altered mental status and vision loss, possibly due to central blindness, were the major symptoms, this dog was suspected of having a forebrain lesion (Wheeler, 1991). The periuria was most likely a secondary problem caused by the decreased mental status.

Hematology, serum biochemistry and analysis of the cerebrospinal fluid (CSF) did not reveal any abnormality.

On MRI, basic T1- and T2-weighted images and a fluid attenuated inversion recovery (FLAIR) sequence were taken. T1-weighted images, where fluids such as CSF color hypointensely, typically provide anatomical information, whereas T2-weighted images, where fluids color hyperintensely, give more information about the actual disease process. A FLAIR sequence is similar to a T2-weighted image, but nulls out "free fluid" so that CSF becomes hypointense instead of hyperintense, and oedema remains hyperintense. The T1-weighted sequence was repeated after the intravenous administration of Magnevist® (Bayer, gadopentetate dimeglumine) for contrast enhancement to detect lesions associated with abnormal vascularity or those thought to alter the blood-brain barrier.

The T1-weighted study showed a hypointense, ill-defined area located in the region of the thalamus, hypothalamus and the caudate nucleus. On the T2-weighted and FLAIR images, this intracranial lesion together with the left optic nerve colored hyperintensely, which revealed left optic nerve infiltration (Figure 1). There was no abnormal contrast enhancement visible on the T1-weighted sequence after the intravenous administration of Magnevist®. Altogether, MRI supported the diagnosis of an intracranial tumor with infiltration of the left optic nerve, and suspicion of a forebrain lesion was abolished.

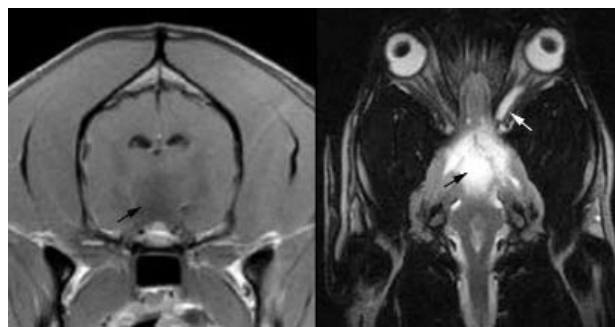


Figure 1. MRI images. The T1-weighted transverse image (left) shows a hypointense ill defined area (black arrow) at the thalamus region. The T2-weighted image in a dorsal plane (right) shows a hyperintense aspect (black arrow) of the intracranial lesion and the left optic nerve (white arrow).

The patient was treated with Prednisolone 5MG® (Kela Laboratoria, Prednisolone, 1 mg/kg p.o. gradually decreased). Since the dog did not make any improvement after 38 days, he was euthanized and necropsied.

Necropsy

Necropsy showed a non-encapsulated extruding white fleshy mass with a diameter of 1.5 cm. This mass was located in the white matter of the ventral thalamic region near the chiasma opticum, and seemed to extend along the left optic nerve (Figure 2). No other brain lesions were detected. Besides congestion of the spleen and lungs, there were no other remarkable abnormalities.

Histology

Hematoxylin and eosin staining revealed a highly cellular intracranial mass of small uniform neoplastic cells with a small basophilic nucleus and a moderate amount of eosinophilic cytoplasm. In the left optic nerve, multifocal infiltration of neoplastic cells was detected. In the brain, the neoplastic cells had a slightly elongated nucleus in contrast to those in the left optic nerve, which had a round nucleus. Both in the brain and in the left optic nerve, the nuclei were surrounded by a perinuclear cytoplasmic vacuole, although the so called 'fried eggs' appearance was only obvious in the latter (Figure 3). The tumoral stroma consisted of fine branching capillaries.

Immunohistochemistry

Immunolabelling for the demonstration of astrocytes (glial fibrillary acidic protein, GFAP, Dako, 1:2000), neurons (neuron specific enolase, NSE, Dako, 1:800; neuron filament, NF, Dako, 1:1000; synaptophysin, Sy38, Dako, 1:400), endothelial cells (von Willebrand factor, Dako, 1:6400; CD31, Dako, 1:5), cell proliferation (Ki67, Dako, 1:20), T-lymphocytes (CD3, Dako, 1:400) and B-lymphocytes (CD20, Dako, 1:400) were performed. Staining was done using the Envision™ System (Dako).

The GFAP staining was clearly positive and showed that the tumor had a large population of non-neoplastic, reactive astrocytes (Figure 4).

Vascularization was demonstrated by the positive labelling of endothelial cells by vWF and CD31. The Ki67 stain showed a low mitotic activity within the tumor. Neoplastic cells did not react in NSE, NF synaptophysin CD3 and CD20 staining.

DISCUSSION

Snyder et al. (2006) studied 173 primary brain tumors in 172 dogs, of which 25 were identified as oligodendrogliomas. The most common presented signs in these animals were seizures (18 dogs), altered mental status (10 dogs) and loss of vision (5 dogs). Other symptoms included neck pain and vestibular symptoms. Although the symptoms seen in the patient of the

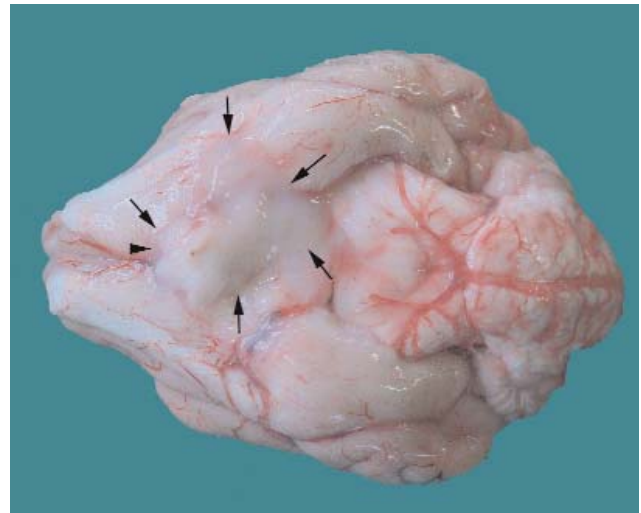


Figure 2. Gross aspect of the ventral brain. This picture shows the presence of a lardaceous mass (delineated by arrows) with infiltration of the left optic nerve (arrow-head).

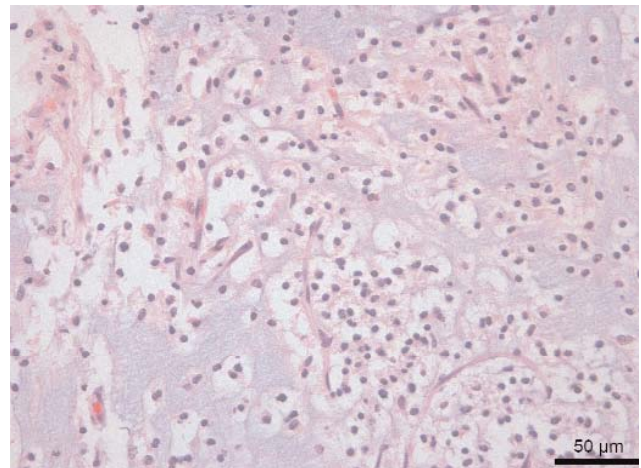


Figure 3. Section of the left optic nerve. Hematoxylin and eosin staining reveals a highly cellular mass of small uniform neoplastic cells with a small basophilic nucleus, a moderate amount of eosinophilic cytoplasm and a perinuclear halo (Fried egg appearance).

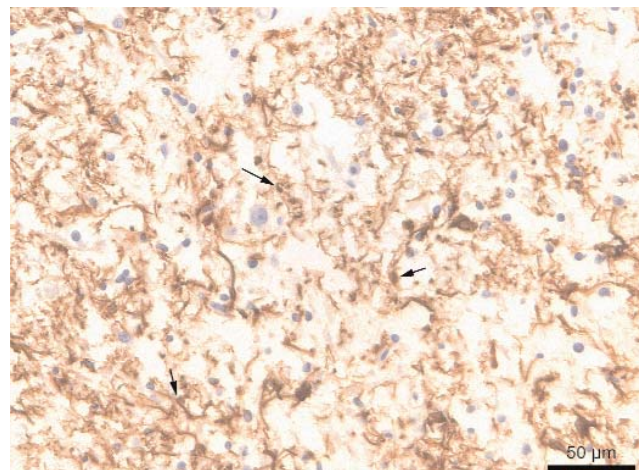


Figure 4. Section of the tumor in the brain. Immunolabelling for GFAP shows the presence of non-neoplastic astrocytes (arrows).

present case did not include epileptic seizures, there were clear signs of an altered mental status and loss of vision of the left eye. In the same study by Snyder et al. (2006), the results of the analysis of CSF fluid of seven dogs diagnosed with oligodendroglioma were reported. In five animals, the protein levels were elevated, and in three dogs the amount of white blood cells was increased. No abnormalities were detected in the cerebrospinal fluid of one dog, similar to the results of the dog in this case. At necropsy, most of the tumors were localized at the telencephalon (twenty dogs) (Snyder et al., 2006). The diencephalon (six dogs), mesencephalon (three dogs), myelencephalon (four dogs) and the olfactory region (five dogs) were less common targets. In half of the cases, the tumor had already stretched out to more than one of these regions. These findings suggest that the localization of the tumor in the thalamic region (which is localized in the diencephalon) in the present case is less common, but not exceptionally rare for this type of tumor.

To the authors' knowledge, the infiltration of the optic nerve by an intracranial oligodendroglioma has not been reported in dogs yet. Naranjo et al. (2008) described a retinal oligodendroglioma with moderate invasion in the optic nerve. In human medicine, oligodendrogliomas originating from the optic nerve are rarely described (Offret et al., 1995; Lucarini et al., 1990). Although the tumor was morphologically classified as grade II, the tumor in the patient behaved rather malignant as neoplastic cells invaded the optic nerve. This probably concerned a slow process given the gradual worsening of the clinical symptoms.

Due to the positive pupillary light reflex, the blindness was suspected to be of central origin. However, no abnormalities were detected in the visual cortex on MRI or at necropsy.

This could be due to two reasons. Firstly, Koch et al. (2011) described a case report of a patient with multifocal oligodendroglioma without abnormalities at MRI or necropsy but with neoplastic cells present at histology. It is possible that the patient of the present case suffered from microscopical neoplastic infiltration of the visual cortex causing central blindness. Unfortunately, this could not be demonstrated. Secondly, it is also possible that the invading neoplastic cells did not destroy the optic nerve completely, resulting in a positive pupillary light reflex.

For the treatment of the patient, a palliative approach was chosen. Other options might have been radiation therapy or radiosurgery (Lester et al., 2001). The first method uses fractionation schemes to minimize the damage, caused by the ionizing radiation, to the surrounding tissues. Radiosurgery operates by directing highly focused beams of ionizing radiation with high accuracy to the neoplastic tissue via a stereotactic head frame. The radiation source rotates in an arc around the tumor, with several noncoplanar arcs. This method allows the use of a larger single treatment dose and thus a lower total dose. It therefore decreases the complications compared to classical radiation therapy. The availability of these treatments as well as the

owner's motivation may have influenced the choice of therapy.

In most cases, an oligodendroglioma has a typical appearance on histology, which is sufficient for the diagnosis. In some cases however, immunohistochemical staining may be necessary to distinguish an oligodendroglioma from other gliomas. In human medicine, the most frequently used primary antibodies for immunohistochemistry in tumors of the central nervous system are neuron-specific nuclear protein (a neuronally specific nuclear protein in vertebrates), synaptophysin (protein of the presynaptic vesicle), neuron-specific enolase (glycolytic isoenzyme in neurons and neuroendocrine cells), high molecular weight microtubule associated protein (required for initial neurite growth), neurofilament protein (intermediate filament found specifically in neurons), glial fibrillary acidic protein (intermediate filament protein expressed by astrocytes), vimentin (intermediate filament expressed by mesenchymal cells) and epithelial membrane antigen (heavily glycosylated transmembrane proteins expressed in several epithelial and non-epithelial cells) (Koperek et al., 2004). A study by Koperek et al. (2004) showed that markers for the detection of neuron-specific nuclear protein, vimentin and epithelial membrane antigen by immunohistochemistry can be used to differentiate a neurocytoma from an oligodendroglioma or ependymoma. Markers for vimentin, epithelial membrane antigen and GFAP can be used to differentiate between an ependymoma and oligodendroglioma. Unfortunately, these markers have not yet been evaluated for canine oligodendrogliomas. Furthermore, a specific antibody for the detection of oligodendrocytes in dogs is not yet available. Therefore, veterinarian pathologists have to rely on the classical histological evaluation of tissue slides combined with immunohistochemistry. In the present case, histological examination revealed cells with a "fried egg" appearance, which was not always typical due to post-mortem autolysis and high numbers of astrocytes as demonstrated by immunohistochemistry. Careful examination revealed that these astrocytes were non-neoplastic and rather reactive, thus complicating the morphological diagnosis. It has been described that oligodendrogliomas may include reactive, proliferating but non-neoplastic astrocytes. When the amount of astrocytes exceeds 30 % of the mass' total cell population, these tumors are classified as oligoastrocytomas (Meuten, 2002).

CONCLUSION

The present case study describes a unique case of a low grade (II) intracranial oligodendroglioma in a dog with infiltration of the optic nerve. The more elongated nuclei in the neoplastic cells in the brain are a point of discussion and make differentiation between an oligodendroglioma and an oligoastrocytoma difficult. The GFAP-negativity of the neoplastic cells favors the first diagnosis. Nevertheless, this case points out the need of a specific immunohistochemical marker for oligodendrogliomas in small animal medicine.

REFERENCES

- Braund K.G. (2005). Nervous system. In: Kahn C.M., Line S., Aiello S.E. (editors). *The Merck Veterinary Manual*, 9th ed., National Publishing Inc., Philadelphia, 979-1081.
- Bullard D.E., Rawlings C.E., Phillips B., Cox E.B., Schold S.C. Jr., Burger P., Halperin E.C. (1987). Oligodendroglioma: an analysis of the value of radiation therapy. *Cancer* 60, 2179-2188.
- Koch M.W., Sánchez M.D., Long S. (2011). Multifocal oligodendroglioma in three dogs. *Journal of the American Animal Hospital Association* 47, 77-85.
- Koestner A., Higgins R.J. (2002). Tumors of the nervous system. In: Meuten D.J. (editor). *Tumors in Domestic Animals*, 4th ed., Iowa State Press, Iowa, 703-706.
- Koperek O., Gelpi E., Birner P., Haberler C., Budka H., Hainfellner J.A. (2004). Value and limits of immunohistochemistry in differential diagnosis of clear cell primary brain tumors. *Acta Neuropathologica* 108, 24-30.
- Kraft S.L., Gavin P.R. (1999). Intracranial neoplasia. *Clinical Techniques in Small Animal Practice* 14, 112-123.
- LeCouteur R.A. (1999). Current concepts in the diagnosis and treatment of brain tumors in dogs and cats. *Journal of Small Animal Practice* 40, 411-416.
- Lester N.V., Hopkins A.L., Friedman W.A., Buatti J.M., Meeks S.L., Chrisman C.L. (2001). Radiosurgery using a stereotactic headframe system for irradiation of brain tumors in dogs. *Journal of the American Veterinary Medical Association* 11, 1562-1569.
- Louis D.N., Ohgaki H., Wiestler O.D., Cavenee W.K., Burger P.C., Jouvet A., Scheithauer B.W., Kleihues P. (2007). The 2007 WHO classification of tumors of the central nervous system. *Acta Neuropathologica* 114, 97-109.
- Lucarini C., Tomei G., Gaini S.M., Grimoldi N., Spagnoli D., Losa M. (1990). A case of optic nerve oligodendroglioma associated with an orbital non-Hodgkin's lymphoma in adult. Case report. *Journal of Neurosurgical Sciences* 34, 319-321.
- Meuten D.J. (2002). *Tumors in Domestic Animals*, 4th edition. Iowa State Press, Iowa, p. 703-706.
- Naranjo C., Schobert C., Dubielzig R. (2008). Canine ocular gliomas: a retrospective study. *Veterinary Ophthalmology* 11, 356-362.
- Offret H., Gregoire-Cassoux N., Frau E., Doyon D., Comoy J., Lacroix C. (1995). Solitary oligodendroglioma of the optic nerve. Apropos of a case. *Journal Français d'Ophthalmologie* 18, 158-163.
- Snyder J.M., Shofer F.S., Van Winkle T.J., Massicotte C. (2006). Canine intracranial primary neoplasia: 173 Cases (1986-2003). *Journal of Veterinary Internal Medicine* 20, 669-675.
- Wheeler S. (1991). The nervous system. In: White R. (editor). *Manual of Small Animal Oncology*. B.S.A.V.A., Gloucestershire, p. 315-340.
- Young B.D., Levine J.M., Porter B.F., Chen-Allen A.V., Rossmesl J.H., Platt S.R., Kent M., Fosgate G.T., Schatzberg S.J. (2010). Magnetic resonance imaging features of intracranial astrocytomas and oligodendrogliomas in dogs. *Veterinary Radiology & Ultrasound* 52, p. 132-141.

Uit het verleden

LONGTERING (TUBERCULOSE) BIJ RUNDEREN

“De longen worden de vergaderplaats van tuberculeuze stof die zich in gezwollen verzamelt en eigenlyk de tuberkels uitmaekt, of die zich in longenweefsel verspreidende, eene tuberkuleuze ophooping uitmaekt. De gezwollen en verzamelingen zyn grys, geelachtig of doofwit; zy zyn van een vasten aerd, spekachtig of week; zy worden langzamerhand weeker, en veranderen in een dik kaesachtig vocht, dat een etter gelykt en schynt te zullen uitbreken. Zy veranderen ook wel in eene krytachtige, witte massa, kalktuberkulose genoemd, en die het byzonder kenteeken van longtering uitmaekt.

Oorzaken. - De erfelykheid van tuberkuleuze stof staet op den eersten rang der oorzaken; men heeft voorbeelden van gansche geslachten van rundieren die er aen gestorven zyn. Men kan ook niet ontkennen dat er ook een lichaemlyk voorbereidsel bestaet; en dat dezelve eigen is aen de koeijen met eenen zwakken lichaamsbouw, fyne, gedweeë en zachte huid, en die, ondanks hare magerheid, overvloedig melk geven.

Behandeling. - Dezelve is slechts schynbaar herstellend; want in geval het dier dat eenige tuberkels en watergezwollen in de longen draegt, eene schynbare gezondheid geniet, dan bestaet hetzelfde niet meer zodra de ziekte tekenen voor den dag komen. Dezelve duiden ongeneesbare ongeregelheden aen.

De rust, het inademen van waterdampen stillen de lonenprikkeling en begunstigen het uitstroomen van de tuberkuleuze verwekte stof. De vetmaking die soms in het begin lukt, is het beste voordeel dat men uit longtering besmette dieren kan trekken.”

Uit: Verheyen, P.S.J. (1857). *Handboek der Veeartsenykunde*, tweede deel, Brussel, pp. 324-325.

Noot van de redactie

Al bij al een vrij accurate weergave van deze ooit sterk verspreide plaag. Uit een hier weggelaten stukje beschrijving van de letsels blijkt dat de ziekte nog niet duidelijk gedifferentieerd werd van echinococose en fascioliasis.

Pierre Joseph Seraphique Verheyen (Vilvoorde 1806 - Kuregem 1964; gediplomeerd in Utrecht) was een van de allereerste professoren aan de eerste Belgische veeartsenijschool in Kuregem (Anderlecht). Zijn handboek dat gelijktijdig in het Frans en het Nederlands verscheen, was in Vlaanderen veel minder verspreid dan dat van de Utrechenaar Numan en de Duitser Wagenfeld.

Luc Devriese