

Cannabinoid oil with gabapentin for the treatment of chronic neuropathic pain – a case report

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Summary

A 3-year-old Leonberger was presented with unilateral atrophy of the left temporal muscle, concomitant left corneal hypoesthesia and jaw pain. Based on magnetic resonance imaging (MRI) results, a trigeminal peripheral nerve sheath tumor was presumptively diagnosed, and treatment based on volumetric modulated arc therapy combined with temozolomide was introduced. Although the tumor volume was stable, after 6 months the patient developed severe jaw pain manifested by rubbing of the face, aversion to eating, and yawning. No desirable response to combinations of meloxicam, gabapentin, tramadol/buprenorphine at their maximal tolerated doses was achieved. Only a treatment based on a commercially available nonpsychoactive cannabinoid oil – Perognidol® (Ilovet) combined with gabapentin successfully relieved the symptoms of pain within a week. Three months later, a follow-up MRI revealed a significant growth of the tumor associated with cerebral infiltration. Eventually, the general condition of the patient deteriorated. The dog was euthanized 800 days after the original diagnosis.

Keywords: trigeminal peripheral nerve sheath tumor, PNST, dog, cannabinoid oil, chronic neuropathic pain

Primary intracranial trigeminal peripheral nerve sheath tumors (PNST) are quite uncommon, especially in young dogs (20). The disease symptoms and their progression are related to unilateral trigeminal nerve dysfunction, with an expected outcome of ipsilateral masticatory muscle atrophy and loss of facial sensation (6). It has been reported that most dogs diagnosed with trigeminal PNST present with atrophy of the temporalis and masseter muscle groups and sometimes facial rubbing behavior or show signs of reduced corneal and facial sensation, the absence of palpebral reflex, decreased menace response, ipsilateral Horner's syndrome, and ptosis (3). All above mentioned symptoms appeared in our patient as the disease progressed. As PNST tumors are known to cause neuropathic pain (7), an accurate, multimodal and patient-adapted treatment is required to improve the quality of life in cancer suffering patients (7, 11, 17). Although the treatment of chronic, neuropathic pain is challenging, non-psychoactive cannabinoid (CBD) oils have shown promise (23).

Case history and diagnostic testing

A 3-year-old Leonberger was presented with unilateral atrophy of the left temporal muscle with concomitant left corneal hypoesthesia in August 2018. The owner reported that the dog recently refused to eat dry pet food and measurements from the clinic revealed a 7% weight loss within 2 months. During an oral cavity examination, mild jaw pain was observed. Clinical and neurological examination did not reveal any additional abnormalities. Muscle atrophy can be explained by neuropathies or myopathies. After thorough physical examination the differential diagnosis was narrowed down to masticatory muscle myositis, idiopathic neuritis, hypothyroidism, post-traumatic trigeminal neuropathy or neoplastic disease, as the most possible causes. Routine laboratory test results (including free thyroxine (fT4) levels) and an abdominal ultrasonography did not reveal any abnormalities. Interestingly, a titer value (1 : 500) of auto antibodies against type 2M fibers supported the initial suspicion of early stage masticatory muscle myositis. After one month of treatment with *per os* (PO) *bis in die* (BID) 2 mg/kg prednisone (with a slowly tapered dose to the lowest every-other-day dose) and thiamine and pyridoxin supplementa-

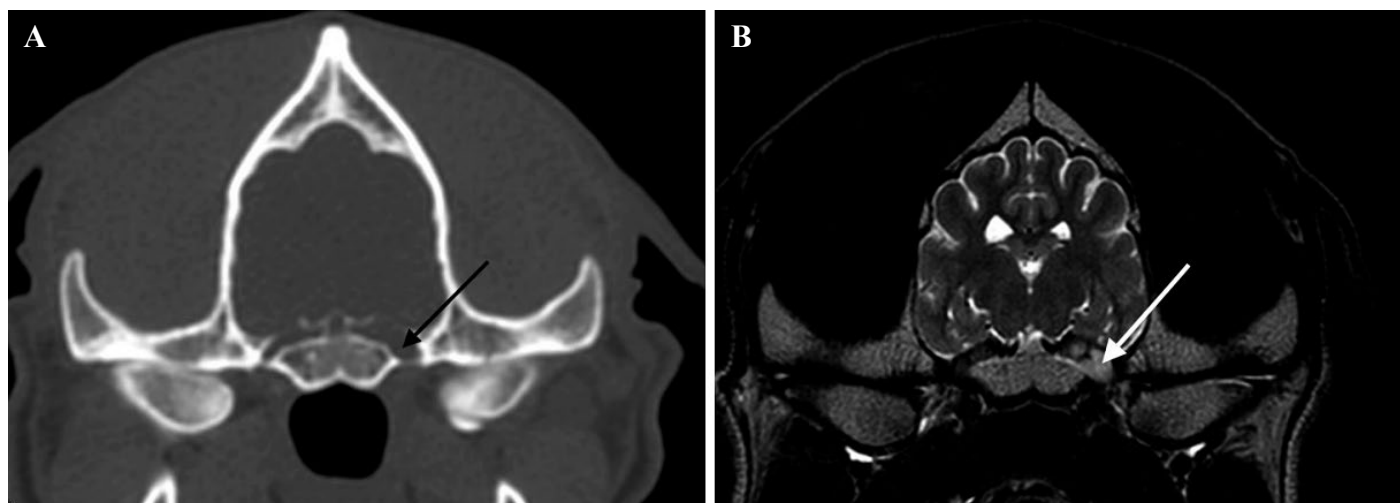


Fig. 1. A. Head CT image in transverse plane. Widening of the left foramen ovale, which contains the trigeminal nerves visible (arrow). **B.** First head MRI T2 weighted image in transverse plane. Hyperintense mass associated with left trigeminal nerve is visible (arrow)

tion, neither improvement nor deterioration were observed. In light of treatment failure, the owners agreed to perform a head computed tomography (CT). A moderate widening of the left oval foramen and mild atrophy of the ipsilateral temporal muscle was seen on the head CT (Fig. 1A). No other abnormalities were noted. Because there was a strong suspicion of cranial nerve pathology, magnetic resonance imaging (MRI) of the brain was performed, which revealed an extra-axial mass with sharp and regular margins in the anatomic location of the trigeminal nerve with involvement of its mandibular branch (Fig. 1B).

The lesion was isointense on T1-weighted images and hyperintense on T2-weighted images and homogeneously contrast enhancing. At the time of the imaging the abdominal ultrasonographic examination was normal.

In the light of the diagnosis of trigeminal PNST the volumetric modulated arc therapy (VMAT) consisting of 37 Gy in five fractions combined with 6 months, chemotherapy based on 75 mg/m² PO temozolomide in 42 days cycles was performed in December 2018 as described by Dolera et al. (6, 16). At the first follow up examination the tumor volume was unchanged and no adverse effects were observed, except for a mild otitis externa 3 weeks post-radiotherapy. A follow-up MRI 6 months after VMAT and chemotherapy revealed a severe worsening atrophy of the left temporal muscle, however the tumor volume was stable. At this time, the patient started to exhibit severe jaw pain manifested by aversion to eating and yawning. Multiple treatments based on 0.2 mg/kg daily meloxicam, or *quaque die* (QD) in combination with 1 mg/kg tramadol or 0.02 mg/kg buprenorphine *ter in die* (TID), or meloxicam combined with 1 mg/kg tramadol TID with 5 mg/kg gabapentin TID and 5 mg/kg amantadine QD were not considerably effective against the neuropathic pain, as determined by failure to relieve the patient's pain. Only a PO BID treatment

based on commercially available nonpsychotic CBD oil (Perognidol[®]; Ilovet) combined with 10 mg/kg gabapentin successfully relieved the symptoms of the patient's persistent neuropathic pain. Over time, a significant progression of muscle atrophy of the left side led to a lack of sensation and function of the left facial area associated with neurotrophic keratitis. When balance disorders combined with anorexia were manifested, the owner allowed a follow-up MRI in May 2020, which revealed severe cerebral edema due to significant growth of the tumor associated with cerebral infiltration (Fig. 2). Furthermore, fluid accumulation occurred in the entire left tympanic bulla due to Eustachian's tube dysfunction, which in turn was secondary to paralysis of the *tensor veli palatini* muscle. The latter is often associated with trigeminal nerve neoplasia because the *tensor veli palatini* muscle is innervated by the mandibular branch of the trigeminal nerve.

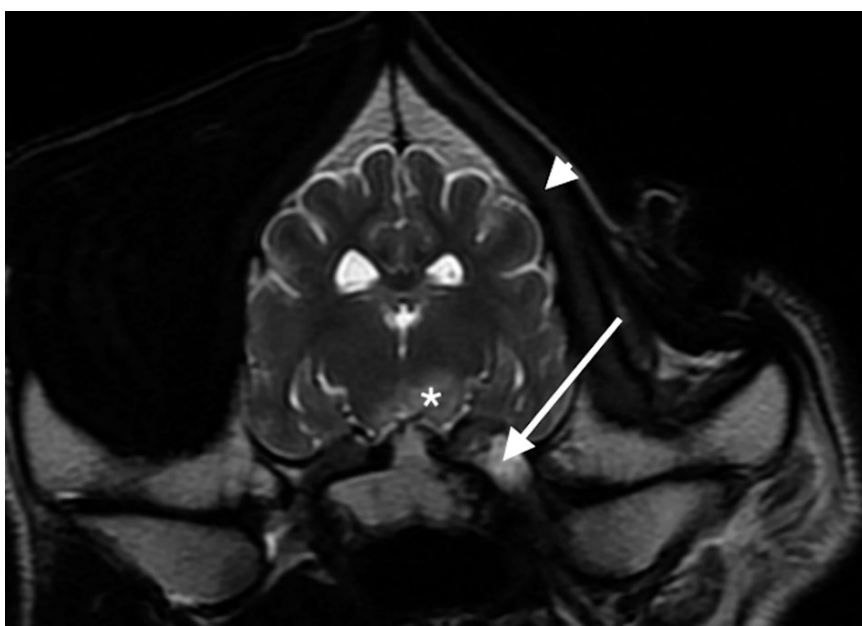


Fig. 2. Last head MRI T2 weighted image in transverse plane. Hyperintense mass associated with left trigeminal nerve is still visible (arrow). Tumor invasion into the brain (asterisk) and severe atrophy of ipsilateral temporal muscle (arrowhead) are now visible

To mitigate the symptoms related to the cerebral edema we introduced a 3-days treatment based on 1 mg/kg methylprednisolone intravenously, which substantially improved the state of the patient, manifested by the disappearance of balance disorders and the patient's willingness to run and play again. A subsequent chemotherapy regimen of 80 mg (68 mg/m³) lomustine in 21 days cycles combined with CBD oil and gabapentin in the above mentioned dosage were effective for 5 months (8 administrations). After this time, in view of the deterioration of the general condition of the patient and the liver insufficiency, the owner chose to euthanize the dog. The patient lived 830 days after the diagnosis of PNST was determined. Regular blood tests throughout the treatment regimens showed hematological and biochemical values were within normal parameters, apart from the one preceding the euthanasia, which indicated a liver insufficiency associated with lomustine treatment. Interestingly, in the course of the chemotherapy based on lomustine the owner reported an appearance of a subcutaneous nodule, from which an adult filarial nematode *Dirofilaria repens* was removed by incision. A blood smear revealed the presence of *Dirofilaria repens* microfilariae in the patient. In this dog, *Dirofilaria repens* infection was likely associated with underlying immunodeficiency, which may have predisposed susceptibility to parasitic infection (22).

Discussion

Few studies concerning canine trigeminal PNST have been published to date, and mostly in small groups of animals (3, 6, 16). It is yet unclear if, or for how long, the VMAT treatment had an effect on the growth of the tumor in our case study. If the patient had regular MRIs check-ups between May 2019 and May 2020 an earlier intervention with lomustine may have prolonged the patient's life. In line with a previously reported canine trigeminal PNST median life expectancy of 952 days (6), our patient survived over 800 days after initial diagnosis. Despite the limited abundance of literature and resources to guide treatment of intracranial trigeminal PNST, the presence of a tumor is clearly associated with chronic neuropathic pain. Identifying efficacious treatment options is, thus, critical to improving the quality of life of affected patients. This case study is the first to describe in detail a comparison of treatment schemes, and identification of a beneficial effect of CBD oil in multimodal oncological palliative treatment, even when curative approaches did not provide a remission of the tumor.

Recognizing and assessing the severity of pain, and hence treatment course, often causes problems for veterinary physicians, especially for chronic pain that develops as a disease progresses (6, 20). Moreover, in oncological patients, clinicians deal not only with the distress caused by the primary tumor, but also with the neuropathic and radiotherapy or chemotherapy induced pain that frequently follows (3, 6, 20). Neuropathic pain assessment in humans is based on self-report, which is impossible to obtain in veterinary patients. Moreover, there is no objective scale that is commonly employed

for this purpose in veterinary medicine. A possible solution that requires further investigation is use of the quantitative sensory testing (QST), a technique developed for laboratory rodents (17). Currently, the evaluation of neuropathic pain in dogs is based on clinical examination and, more importantly, a proactive history from the owner (17). Typical signs associated with this condition in dogs are: altered reaction to touch, vocalization, excessive scratching or licking, decreased activity, lack of appetite and changes in general behavior (17). In the current case study, symptoms of neuropathic pain associated with the trigeminal tumor infiltration observed by the owner were mostly rubbing of the face, lack of appetite, avoidance of eating dry food and yawning.

The use of monotherapy nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids, or in combination, was completely ineffective in managing symptoms of neuropathic pain in our patient. This may be due to the fact that the neuropathic pain is usually nonresponsive to standard analgesics and requires multimodal analgesic protocols (7, 17, 20). Neuropathic pain is observed in cases of tumors that directly affect nervous tissue, such as nerve sheath tumors, but can also result from radio- and chemotherapy (3). The combination of meloxicam, buprenorphine and gabapentin was a sufficient treatment for some time, but it was impossible to phase out other drugs and continue with gabapentin alone. Moreover, after the breakthrough period this treatment scheme also seemed insufficient, as the pain-related signs recurred and the quality of patient's life deteriorated.

In humans, CBDs are increasingly being studied for the treatment of chronic pain in cancer patients, although their use has not yet become a standard procedure (11). Several cannabis-based veterinary products have recently appeared on the market, prompting a growing interest in their use in companion animals (6). However, there are few clinical reports describing the effectiveness of these drugs in veterinary patients, and indications for their use are primarily extrapolated from human medicine (6).

The Government of Canada published a comprehensive review of the scientific literature on the effects of cannabis and CBD intended for health care professionals (1). This review is aimed at human medicine, however the guidelines may also be beneficial in veterinary practice. According to the authors statement, CBD can be useful in palliative treatment, as it exhibits an antinociceptive effect in animal models of chronic pain (inflammatory and neuropathic) and can alleviate symptoms of osteoarthritis and rheumatoid arthritis (1). This topic has also been recently reviewed from the perspective of veterinary medicine in context of general therapeutic prospects (1) and palliative treatment in cancer patients (19).

There are two main populations of CBD receptors: CB1 and CB2 (13). CB1 receptors are located primarily

in the central nervous system while CB2 receptors are located mostly peripherally (13). Stimulation of CB1 receptors is responsible for psychotropic effects of cannabis, but this receptor is also engaged in the control of pain, nausea, mood and anxiety (14). CB1 receptors are also present at lower, but functionally significant levels in the peripheral tissues (14, 18). These were reported to play an important role in peripheral and central processing of nociceptive messages (13). The commercial product we used, Perognidol® (Ilovet), contains the CBD cannabinol, a non-psychotropic whose effect on CBD receptors remains unclear. Initially cannabinol was found to display antagonistic activity at CB1 and CB2 receptors (2) but with a very low affinity to both receptors (18). It also exhibits a physiological modulating effect through non-CB receptors and ion channels, and is involved in inhibiting the activity of enzymes responsible for the breakdown of endogenous CBDs (2, 12).

The bioavailability of cannabidiol in dogs is quite poor and depends on product formulation; however, our use of 10 mg/kg gabapentin with manufacturer recommendations of PO BID Perognidol appeared to elicit a therapeutic effect. Several other studies have reported efficacy of CBD formulations with varying degrees of bioavailability. In a clinical trial conducted in healthy dogs, a CBD-infused oil formulation, in comparison to micro encapsulated oil beads or CBD-infused transdermal cream, resulted in the highest maximal CBD plasma concentrations and showed the smallest inter-individual variability (4). In combination with other medication, CBD has been shown to be effective in relieving osteoarthritic pain in dogs (5). Furthermore, dogs receiving oral transmucosal cannabidiol in addition to an anti-inflammatory drug showed a noticeable improvement, in comparison with dogs that did not receive cannabidiol. In another study, the treatment with CBD-based oil alone, was sufficient to alleviate the pain related to osteoarthritis in dogs (8). CBD was also reported to suppress chronic inflammatory and neuropathic pain in rodents, without causing negative side effects or tolerance issues (23).

The product (Perognidol®), used for palliative treatment in our case, is a 10% CBD oil-based formulation, including medium chain fatty acids that can facilitate increased bioavailability of CBD. Apart from CBD, this product also contains docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish oil which display synergistic anti-inflammatory and neuro protective effects and *Commiphora myrrha* resin extract, that has been reported to have analgesic properties (9, 21). In our presented case study, the combination of a commercial product Perognidol® and gabapentin was effective in relieving pain and maintaining a quality of life in the patient for over eight consecutive months, illustrating the effectiveness and potential for CBD-based therapeutic approaches in dogs. While more evidence-based data is required to develop standard-

ized treatment schemes, it is a promising prospect for managing chronic pain in small animals, especially when neuropathic pain component is suspected.

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