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Pain or anxiety: the case of a 12-year-old German Shepherd

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Abstract: A 12-year-old, 25 kg (BCS 3/5), intact female German Shepherd was evaluated for sudden manifestations of intense fearful behavior with no apparent triggering stimulus. The dog had a history of aggressive behavior towards conspecifics and, more recently, fearful behavior in response to loud noises. Furthermore, the dog suffered from bilateral hip dysplasia and had recently been diagnosed with multiple severe spinal compressions at both lumbar and thoracic level. Various attempts to treat pain were made, with no success. Soon after, the dog began to display intense fearful behavior without apparent reason. At first, this behavior occurred only in unfamiliar indoor environments. However, it rapidly generalized to other contexts, to the point of being displayed almost constantly. A behavioral evaluation was requested. CBC, serum biochemical analysis, thyroid profile and echocardiographic examination were unremarkable. The dog's behavioral diagnosis consisted of pain, generalized anxiety and noise sensitivity. Gabapentin dosage was doubled (24 mg/kg BID) and a Fentanyl patch was applied to the dog's back for three consecutive days. No improvement was observed. Hence, Clomipramine was added to Gabapentin at a starting dosage of 0.6 mg/kg BID and titrated to 1 mg/kg after 21 days. After 1 week the owner reported an initial reduction in the frequency and intensity of the fearful behavior which completely disappeared after 1 month of treatment. Mild urinary retention was observed as a possible collateral effect of Clomipramine. Gabapentin dosage was decreased to 20mg/kg BID. With due monitoring of behavioral and physiological parameters, Clomipramine and Gabapentin administration will not be interrupted.

Key Words: dog, anxiety, pain.

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Presentation

A 12-year-old, 25 kg (BCS 3/5), intact female German Shepherd was evaluated for sudden manifestations of intense fearful behavior with no apparent triggering stimulus.

History and presenting signs

The dog was adopted at 5 years of age. The owner found her as she lived as a stray in a semi-rural environment. No information on her history before adoption is available. At the time of adoption she was visibly ill. She appeared extremely emaciated (BCS 1/5), sensory depressed, with diffused alopecia and mucocutaneous erosive-ulcerative lesions, as well as bilateral purulent lesions on her ear pinnae. The dog was diagnosed with Leishmaniosis. Treatment with Meglumine antimoniate (100 mg/kg/die SC for 40 days) and Allopurinol (10 mg/kg PO q12h for 12 months) and local cleaning and disinfection of skin lesions were effective at normalizing the electrophoretic curve and resolve the clinical signs of the disease.

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The owner described a very inhibited dog at the beginning. However, her behavior changed during her physical recovery. She started to display defensive aggressive behavior towards other dogs. She would actively approach other dogs as if she was willing to interact, but she would growl and snap if they got too close, were too aroused, or try to insistently sniff her genital area. With the help of a dog trainer, the owner progressively learned in what circumstances he could let the dog interact with conspecifics and the aggressive behavior eventually disappeared.

During the third New Year's Eve after adoption, the dog displayed extreme signs of emotional distress in response to fireworks. She trembled, hyperventilated and tried to hide in different rooms of the house. During the same period, the dog began to show the same fearful behavior in response to thunderstorms.

Over time, she began to display avoidance behavior towards open windows and indoor air currents. However, since the fearful behavior was mainly manifested during spring and summer season and could be partially prevented by keeping the windows closed, the owner did not seek professional advice.

Starting from the dogs 11th year of age, her behavioral reactions to loud noises became progressively less frequent and intense. The owner reported that such improvement could be chronologically correlated with an overall decrease in the dog's auditory perception. Nonetheless, the dog kept showing hypervigilance and avoidance behavior when windows were open, as well as a mild state of alert during New Years' Eve fireworks.

At 9 years of age, Rx exams were performed because of intolerance to physical exercise and lameness. Bilateral hip dysplasia and several vertebral osteophytic proliferations at lumbar and thoracic level were found. In addition, from the neurological evaluation a cauda equina syndrome was suspected. Further diagnostic tests were recommended in order to confirm the diagnosis, but they were declined by the owner for financial reasons. Therefore, Firocoxib 7 mg/kg/die was prescribed to relieve pain in the short term, alongside with nutritional supplementation with PEA, Quercetin, Omega-3 fatty acids, VIT. E, Glucosamine and Chondroitin sulfate for chronic pain management. After 2 weeks lameness had disappeared and physical activity was back to previous levels.

At 12 years of age, a neurological evaluation was performed because the dog was unable to maintain standing position for long periods of time and started to show ataxic ambulation. The physical examination revealed hind-limb muscle atrophy and proprioceptive deficit, as well as lumbar and coxo-femoral pain. The DNA test for degenerative myelopathy was negative. Prednisolone was prescribed at 0.5 mg/kg/die for 8 days. However, no therapeutic effect was observed. Therefore, a MRI was performed. Three severe medullar compressions at T13-L1, L1-L2 and L2-L3, plus multiple smaller compressions throughout the column were observed. Since a spinal surgery presented high risks for the dog's quality of life and was unlikely to lead to resolution, the owner was advised to start a chronic pain management therapy and prevent the dog from having long walks, as well as performing sudden and unusual movements. The drug therapy consisted of CBD oil 10% solution (8 drops q12h), Gabapentin (12 mg/Kg BID) and Firocoxib (7 mg/kg/die for 10 days).

However, after 30 days the dog had only inconsistently improved. In addition, she started to display behaviors indicative of acute fear such as trembling, tachypnea, hypersalivation and restlessness, ears pulled back, crouched position, hiding behavior and attention seeking. At first, these events occurred exclusively in unfamiliar indoor environments (friends' houses, restaurants, hotel rooms) and the dog would usually calm down once back at home. However, their frequency increased rapidly and after two weeks the dog would display these behaviors almost constantly, both indoor – including her own house- and outdoor. In addition, she would wake up in the middle of the night panting and seeking for proximity and physical contact. The owner reported that there was no association between fearful behavior and presence of open windows or loud noises.

Physical and laboratory evaluation

During the first behavior consultation, the dog remained seated in the same place for most of the time. Body language was characterized by crouched position, hypervigilance, ears pulled backwards, trembling, tachypnea, and hypersalivation. A few times the dog seemed to try to lie down, but quickly returned to a seated position. Posterior lameness, hind limb ataxia and rigid gait and movements were also observed. CBC, serum biochemical analysis, protein electrophoresis, thyroid profile (TT4, FT4 and TSH) and echocardiographic examination were unremarkable.

Diagnosis

There is little doubt that the dog of this report felt pain. Signs of pain were clinically evident and they could be easily elicited by mild manipulation of the back and the hind limbs. All the behavioral signs the dog manifested have been linked with pain in previous studies (Mills et al., 2020). It has been suggested that pain may play a role in the development of aggressive behavior towards other dogs (Camps, 2012), sound sensitivity (Lopes Fagundes et al., 2018), and in the onset of anxious states (Camps et al., 2019) and sleep-wake cycle disorders (Camps et al., 2019).

Although this dog was unsuccessfully treated for pain, there are many conditions in which the analgesic treatment may not lead to a behavioral change, even when pain is somehow involved. In some cases pain may have caused a certain behavior to develop, but may no longer be present. Nonetheless, even when pain is still present, the dog may have developed, over time, negative associations with pain-inducing stimuli. In such cases, the psychological component may mask the effect of a pain management therapy or, at least, longer treatment times may be required in order to extinguish the negative association and lead to behavioral resolution. Sometimes, pain may just be a concurrent cause of the behavior or may be responsible for exacerbating a pre-existing behavioral problem (Mills et al., 2020). In such cases, partial behavioral improvement may be observed if pain medications are administered. Furthermore, not all types of pain and not all individuals equally respond to all types of analgesic medications. This means that we have to assess the type of pain involved as accurately as possible in order to choose the right analgesic drug or combination of drugs (Epstein et al., 2015). Secondly, we may need several attempts with different molecules before we can observe a behavioral response. Lastly, as in the present case, if a positive effect is not achieved, we may still not be able to exclude pain from our differential diagnoses.

The link between pain and anxiety is widely recognized in human medicine (Asmundson & Katz., 2009). It has been suggested that chronic pain may alter an individual's associative learning processes. Individuals in pain may have a reduced ability to identify and discriminate specific pain-eliciting stimuli and may rely, instead, on overall contextual cues. This loose and inaccurate association between pain and perceived threat may not only generate a constant sense of hypervigilance and emotional distress, but may result in an overgeneralization process of the threatening stimuli (Harvie et al., 2013), which in turn promotes anxiety (Meulders et al., 2013). Furthermore, both human and non-human animals that feel pain have been reported to show a pessimistic judgment bias. That is, they tend to perceive a neutral stimulus as potentially negative (Weary et al., 2019). Indeed, this may induce a state of constant fear and emotional distress. Regardless of the mechanism through which anxiety develops, anxious individuals may have an amplified perception of the intensity of pain, caused by constant somatic tension and augmented attentional focus towards painful stimuli (Rhudy & Meagher, 2000).

The quick increase of the contexts in which the dog of this report would display signs of fear was believed to be caused by a pain-induced overgeneralization of the threatening stimuli, which led to a state of generalized anxiety.

In the last few years, noise reactivity was limited to New Years' Eve fireworks. This was possibly due to an aging-related decrease in auditory acuity. However, the dog still manifested hypervigilance and avoidance towards open windows and indoor air currents, which most likely developed as an anticipatory response to the subsequent loud noise of the window banging. Therefore, although not presented at the time of the evaluation, noise sensitivity was diagnosed based on the dog's history and noise-related anticipatory behavior.

Noise sensitivity, pain and anxiety may be strongly related (Lopes Fagundes et al., 2018). A recent study found that the age of onset on noise sensitivity for dogs with painful conditions was higher than that in dogs with no painful conditions. For the former, it was 6.6 years on average, which is approximately the same as that of the dog of this report. Furthermore, amongst dogs with painful conditions there was a higher tendency to generalize their response to a wide range of contexts (Lopes Fagundes et al., 2018), which, as mentioned above, may result in chronic emotional distress.

Despite the dog's age, cognitive dysfunction syndrome was deemed unlikely, as no clinical signs of cognitive impairment could be observed.

Treatment

A last attempt to see whether pain treatment could alleviate behavioral symptoms was made by applying a 75 mcg/h Fentanyl patch at the base of the dog's shaved neck for three consecutive days. In addition, Gabapentin dosage was increased to 24 mg/kg BID, in an attempt to alleviate signs of anxiety and further reduce pain (Crowell-Davies et al., 2019; Lansdberg et al., 2013). Fentanyl is potent mu opioid receptor agonist used for the treatment of spinal and osteoarticular pain in dogs (Egger et al., 2007; Bellei et al., 2011). Gabapentin is a GABA analogue used for neuropathic pain, seizures and anxiety, in dogs (Landsberg et al., 2013). It may have different dose ranges in relation to the purpose of its use. The dose range for neuropathic pain may be slightly narrower (10-20 mg/kg q8-12h) (Moore, 2016) than that for anxiety (10-30 mg/kg q8-12h) (Landsberg et al., 2013).

Behavioral intervention focused on preventing exposure to known threatening stimuli, reduce physical activity and make routine predictable. Windows had to be kept closed at all times. Whenever windows had to be opened (i.e. house-cleaning procedures), the dog had to be brought in a room predisposed with a dog's bed, food-filled toys or problem solving games. Walks had to be kept short and limited to place known to the dog. The owner was also advised not to take the dog to unfamiliar indoor places, such as restaurants or friends' house. Car trips also had to be avoided.

Follow-up

After 10 days the owner reported only mild improvement in the duration of the signs of anxiety, mostly related to a quicker onset of sleep after the administration of Gabapentin. No positive effect of the Fentanyl patch was observed, neither on behavior nor ambulation. Management therapy was implemented but did not appear to be effective at reducing signs of anxiety in any circumstances. Since improvement was not satisfactory and the dog's quality of life was still poor, Clomipramine was started at 0.6 mg/kg BID and increased to 1 mg/kg BID after 3 weeks. Clomipramine is a Tryciclic Antidepressant (TCA) used for the treatment of noise phobia and different forms of anxiety, in dogs (Crowell-Davies et al., 2003; Landsberg et al., 2013). Furthermore, in human medicine, TCA have a demonstrated analgesic effect on peripheral neuropathic pain (Dharmshaktu et al., 2012). Their effect is synergistic if administered in conjunction with Gabapentin (Gilron et al., 2009).

After 7 days from the first Clomipramine administration the dog's behavior had already improved. Overall, her signs of anxiety had decreased in frequency and intensity. She would no longer show any sign of emotional distress when outside for routine walks. When anxious behavior occurred inside the house, the owner would take her to her room, ask her to lie on her bed and remain in her proximity for a few minutes. That appeared sufficient to calm her down.

After 4 weeks the owner reported that the dog's anxious behavior had completely disappeared and ambulation had also improved. However, the owner was reminded that the dog suffered from both a degenerative articular disease and severe spinal compressions that could only worsen over time, and that preventative measures concerning physical activity had to be implemented for the rest of the dog's life. Night awakenings would still occur constantly but only to change posture or go to drink.

Since no signs of anxiety had been observed for 10 weeks, the owner was suggested to leave the door of the room open during cleaning procedures to see whether the dog still reacted to wind currents or open windows. The dog did not show any sign of interest nor alert to open windows. She would finish her food-filled toys and go to bed. Gabapentin dosage was reduced to the maximum dosage reported for neuropathic pain treatment (20 mg/kg BID). Mild urinary retention appeared as a probable collateral effect of Clomipramine administration. Since it was not considered risky no adjustment of the dosage were made.

After approximately 3 months from the beginning of the therapy a first attempt to take the dog to a friend's house was made. The owner was recommended to provide the dog with her own bed once in the car and in the unfamiliar environment. Fortunately, no signs of distress were observed.

At the last follow-up visit, about 5 months after the beginning of the therapy, the dog's ambulation had slightly worsened, compatibly with her pathological condition. However, CBC, serum biochemical analysis and urinalysis were still unremarkable. Signs of anxiety had no longer been observed, neither in outdoor nor in indoor spaces, even if unfamiliar to the dog. Again, the owner was recommended to keep levels of activity to a minimum. With due monitoring of behavioral and physiological parameters, this dog will remain under psychopharmacological treatment for the rest of her life.

Conclusion

There may be a strong relationship between pain and emotional disorders. Although we cannot be certain about it, it is likely that the pathogenesis of the anxious behavior of this dog involved pain at some level. Complete resolution of behavioral signs was achieved by treating the dog with the TCA Clomipramine. Gabapentin was only mildly effective at reducing anxiety symptoms. However, its administration was continued as an additional mangament therapy for neuropathic pain.

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Dolore o ansia: il caso di un Pastore Tedesco di 12 anni

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Sintesi

Un Pastore Tedesco di 25 Kg (BCS3/5) e di 12 anni di età è stato valutato per manifestazioni di paura improvvisa senza apparenti stimoli elicitanti.

Il cane presentava una storia pregressa di aggressioni verso conspecifici e, più recentemente, paura nei confronti di rumori forti. Il cane soffriva inoltre di displasia bilaterale delle anche e gli erano state recentemente diagnosticate compressioni multipli ed importanti a livello delle vertebre toraciche e lombari.

Diversi tentativi furono eseguiti in passato per trattare il dolore ma senza successo. Subito dopo il cane cominciò a manifestare segni di paura senza apparente ragione. All'inizio questo comportamento si manifestava in ambiente interni non familiari ma rapidamente si generalizzò ad altri contesti, fino a mostrarlo praticamente in modo costante.

A questo punto fu richiesta una valutazione comportamentale. CBC, analisi biochimiche, profilo tiroideo e esame ecocardiografico risultarono nella norma.

La diagnosi comportamentale consisteva in sindrome da dolore, ansia e sensibilità ai rumori. Il dosaggio del Gabapentin fu raddoppiato (24 mg/kg BID) e un cerotto di Fentanyl fu applicato sulla schiena dell'animale per tre giorni consecutivi.

Non fu osservato nessun miglioramento e quindi fu aggiunta al Gabapentin la Clomipramina, ad un dosaggio iniziale di 0,6 mg/kg BID, aumentato poi a 1 mg/kg dopo 21 giorni.

Dopo una settimana di trattamento il proprietario riportò un'iniziale riduzione nella frequenza ed intensità dei comportamenti di paura che scomparvero completamente dopo un mese di trattamento. Una lieve ritenzione urinaria fu osservata come effetto collaterale della Clomipramina. Il dosaggio del Gabapentin fu ridotto a 20 mg/kg BID. Con il dovuto monitoraggio dei parametri fisiologici e comportamentali, a somministrazione di Clomipramina e Gabapentin non fu interrotta.