Case-report

Acetazolamide-responsive paroxysmal dyskinesia in a 12-week-old female golden retriever dog

Emilie Royaux[a*], Sofie Bhatti[a], Robert Harvey[b], Laurent Garosi[c], G. Diane Shelton[d], Luc Van Ham[a]

[a]Department of Small Animal Medicine and Clinical Biology, Ghent, University, Belgium; [b]Department of Pharmacology, UCL School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK; [c]Davies Veterinary Specialists, Higham Gobion, Hertfordshire, England, UK; [d]Department of Pathology, School of Medicine, University of California San Diego, La Jolla, CA USA.

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A twelve-week-old female intact golden retriever weighing 6 kg was referred with an 8-week history of recurring episodes of muscle stiffness and collapse. Episodes were most often triggered by excitement and exercise. An episode began with a stiff gait and arched spine progressing to holding the head down and raising the rear. Finally, the dog collapsed with all four limbs extended (Figure 1a-i). After removal of the triggering factor, muscle tone returned to normal and the episode ended. Mentation was normal and abnormal autonomous activity was not present during the entire episode. The dog appeared to be completely normal immediately before and after the event. Frequency of episodes varied from 1-8 per day. Duration of the episodes varied from a few seconds to a maximum of ten minutes depending on the presence of the trigger.

On clinical examination a poor body condition score was noted (2/5). Complete neurological examination revealed generalized muscle atrophy. Patellar reflexes of both pelvic limbs were weak. During the neurological examination the puppy's gait was completely normal. Another puppy was introduced and an episode was triggered. The neurological syndrome was described as an excitement induced hypertonicity with involuntary muscle contractions. A neuromuscular disease or a CNS disorder resulting in a paroxysmal dyskinesia was suspected. The results of a complete blood count (CBC), serum biochemistry and electrolyte analysis were within normal ranges and the pre- and postprandial bile acid concentrations were normal (Na 146 (146-153 mmol/l), K 4.2 (4.0-5.5 mmol/l), Cl 115 (105-117 mmol/l), Ca 2.63 (2.07-2.82 mmol/l), P 1.56 (1.00-1.93 mmol/l), urea 4.7 (1.2-8.5 mmol/l), creatinine 46 µmol/l (increased if > 60 plus bodyweight), total protein 64.9 (55.0-78.0 g/l), albumin 39 (22-44 g/l),

AST 26 (<40 U/l), ALT 24 (<52 U/l), Gamma-GT 5 (<8 U/l), ALP 44 (< 123 U/l), bile acids (pre-prandial) 12 (< 19 µmol/l), bile acids (post-prandial) 5 (< 19 µmol/l) glucose 3.9 (3-5 mmol/l)).

Electromyography was performed during an episode of hypertonicity on the awake dog. Normal motor unit action potentials were seen thereby excluding congenital myotonia. Complete electrodiagnostic testing including electromyography, measurement of motor nerve conduction velocity and measurement of compound muscle action potential following repetitive nerve stimulation was performed under general anesthesia and no abnormalities were found. Muscle biopsies were collected from the cranial tibial, triceps and semitendinosus muscles and were either immersed into 10% buffered formalin or kept chilled and sent by an express service to a specialized laboratory. Upon receipt muscle biopsies were either flash frozen in isopentane precooled in liquid nitrogen or paraffin embedded. Type 2 fiber atrophy or hypotrophy was recognized using the myofibrillar ATPase reaction for fiber typing at pH of 9.8 (Figure 2). Type 2 fiber atrophy in this case may be the result of disuse or altered patterns of neural excitability to the muscle fibers. The affected puppy, unaffected littermates, the dam and the sire all tested negative for the BCAN microdeletion that results in episodic falling syndrome in CKCS (Forman et al. 2012, Gill et al.. 2012). The parents and littermates did not show any signs of hypertonicity.

The puppy was treated with oral clonazepam (0.5 mg/kg BW q. 8 hours per os) for 2 weeks. Treatment with clonazepam did not influence the episodes. After 2 weeks, clonazepam was stopped and was immediately switched to oral acetazolamide (4 mg/kg BW q. 8 hours per os). Three days after the start of acetazolamide treatment, the episodes disappeared completely. Now, one year later, the dog still receives the same dose of acetazolamide and is neurologically normal. The body score is normal and muscle atrophy disappeared. Repeated blood examinations (CBC, serum biochemistry, electrolytes) during the last year were normal. The owner did not report any side effects of long-term acetazolamide treatment.

Paroxysmal dyskinesias are a relatively rare but well-documented group of movement disorders in human medicine and they are also increasingly recognized in veterinary medicine (Woods 1977, Herrtage and Palmer 1983, Blakely and Jankovic 2002, Shelton 2004, Black et al. 2013, Urkasemsin and Olby 2014). This group of movement abnormalities is characterized by sudden occurrence of abnormal involuntary movement that recurs episodically and lasts only for a brief duration (Bhatia 2011). The episodes are distinguished from seizures by the presence of a normal consciousness, absence of autonomic signs and pre– and postictal signs, although an EEG would be necessary to definitively determine this (Jankovic and Demirkan

2002).

In human medicine, paroxysmal dyskinesias are classified in four major groups: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinisegenic dyskinesia (PNKD), paroxysmal exercise induced dyskinesia (PED) and other miscellaneous episodic movement disorders such as the different types of episodic ataxia (Bhatia et al. 2011). They are classified based on their clinical symptoms, genetics, pathophysiology and response to treatment. PKD episodes are triggered by sudden movement and are brief (Bhatia et al. 2011). The clinical manifestation can be chorea, dystonia, ballismus or a combination of those. Patients may have several attacks a day. They respond well to anticonvulsant therapy (Houser et al. 1999, Bruno et al. 2004). PNKD episodes have a longer duration than PKD episodes. Attacks happen less frequently (few times a year up till several times a week). They are triggered by coffee, tea, and strong emotions (Bhatia et al. 2011). The most described clinical manifestation is a combination of dystonia and chorea (Bhatia et al. 2011). Response to anticonvulsant treatment is limited. Patients should be taught to identify triggering factors (Forssman 1961, Lance 1963, Bressman et al. 1988). Dog owners can learn to avoid situations that trigger an episode. PED is triggered by physical exhaustion after continuous exertion (Lance 1977). Most described clinical feature is dystonia (Bhatia et al. 1997, Plant et al. 1984). A ketogenic diet is beneficial for PED, some patients respond well to gabapentin, levodopa, acetazolamide and trihexiphenidyl (Bhatia et al. 1997, Weber et al. 2009).

Hypertonicity syndrome is a specific group of paroxysmal dyskinesias (Shelton 2004). Clinically hypertonicity syndrome is characterized by episodes ranging from ataxia to inability to stand as a result of muscle hypertonicity (Shelton 2004, Park et al. 2014). Hypertonicity syndrome was first observed in young Scottish terriers and known as Scottie cramp (SC) (Meyers et al. 1970, Meyers et al. 1973, Clemmons et al. 1980). Similar clinical signs are seen in Cavalier King Charles spaniels (CKCS) with episodic falling syndrome (EFS) (Herrtage and Palmer 1983) and border terriers with canine epileptoid cramping syndrome (CECS) (Black et al. 2013). Case reports of dalmatians (Woods 1977), springer spaniels (Shelton 2004), wheaton terriers (Shelton 2004) and a Yorkshire terrier (Park et al. 2014) with similar clinical signs have also been described.

An abnormality in central nervous system (CNS) neurotransmission was suspected in CKCS and a microdeletion in the brevican gene (*BCAN*) was identified (Forman et al. 2012, Gill et al. 2012). Brevican has an essential role in the formation of perineuronal nets governing synapse stability and nerve conduction velocity (Gill et al. 2012). Scotty cramp is associated with a relative deficiency of the inhibitory neurotransmitter serotonin (Meyers et

al. 1973). A presumptive diagnosis is made based on clinical signs and breed. The episodes are distinguished from seizures by the presence of a normal consciousness, absence of autonomic signs and pre– and postictal signs, although an EEG would be necessary to definitively determine this (Jankovic and Demirkan 2002). Various forms of paroxysmal dyskinesia described up to now might not represent the same entity, therefore response to treatment may vary. Most of the CKCS with EFS were reported to respond well to clonazepam (Garosi et al. 2002). The carbonic anhydrase inhibitor, acetazolamide, was also described as having therapeutic benefit in these dogs (Platt 2014). Almost 50% of border terrier dogs with CECS respond well to dietary adjustments with gluten free diet (Black et al. 2014). Treatment of SC consists of daily oral dosing with acepromazine maleate or diazepam, also vitamin E and serotonin reuptake inhibitors such as fluoxetine may be useful in affected dogs (Clemmons et al. 1980, Shelton 2004, Geiger and Klopp 2009, Platt 2014, Urkasemsin and Olby 2015). Here we describe a hypertonicity syndrome in a young female golden retriever. To the author's knowledge, no similar case in this breed has been reported to date.

The young age of onset at 3-4 months, episodes of hypertonicity and collapse, the normal behavior between episodes, the frequency and the duration of episodes which depended on the presence of a stressful triggering factor is similar to the hypertonicity syndromes that was previously described as episodic falling in the CKCS or cramping in the Scottish terrier (Meyers et al. 1970, Herrtage and Palmer 1983). The diagnosis of a paroxysmal dyskinesia was based on the clinical signs that were inconsistent with epileptic seizures.

On neurological examination generalized muscle atrophy and weak patellar reflexes were found. To examine the neuromuscular part of the nervous system, an electrophysiological examination was performed. However, no abnormalities were detected, making a primary neuromuscular disease less likely. Histopathological examination of muscle biopsies excluded a primary myopathy. Myofiber size variation that could indicate variability in neuronal excitability was detected. In human medicine, some paroxysmal dyskinesias are caused by an ion channelopathy. An ion channelopathy can cause increased neuronal excitability that leads to paroxysmal dyskinesias (Wei et al. 2005). Phenotypically the episodes of the puppy were similar to those of the CKCS with EFS. Therefore the puppy, the parents and the littermates were screened for the *BCAN* mutation that is associated with EFS in the CKCS. All dogs tested negative excluding the CKCS EFS microdeletion as a cause of this disorder. This finding does not rule out the possibility of another mutation in the *BCAN* gene resulting in this syndrome in the golden retriever. Further genetic testing including sequencing of the *BCAN* gene would be necessary to identify an underlying mutation.

The episodes in this case were triggered by excitement and stress, and as such, may be classified as PNKD. Avoiding excitement and stress could be part of the treatment but that would negatively affect the life quality of the dog. Therefore medical treatment was tested. Clonazepam, a successful therapy in CKCS with EFS, was not successful in this case. It was reported that some CKCS with EFS responded to the carbonic anhydrase inhibitor acetazolamide, but information concerning this treatment is limited (Platt 2014). Treatment of the golden retriever puppy with acetazolamide resulted in complete remission of clinical signs. The main biochemical action of acetazolamide is the inhibition of carbonic anhydrase resulting in kaliuresis, diuresis and metabolic acidosis (Zarosin et al. 1983). Acetazolamide also lowers serum bicarbonate levels and reduces the amount of brain lactate and pyruvate, resulting in subsequent brain acidosis (Zarosin et al. 1983) and changes in intracellular and extracellular pH. The change in pH alters the membrane potential which finally results in decreased neuronal excitability (Spacey et al. 2004). In human medicine, acetazolamide is used for many different non-neurological and neurological diseases such as epilepsy, hypokalemic periodic paralysis, myotonia congenita, episodic ataxia and other paroxysmal dyskinesias (Neufeld 2009, Vroom et al. 1975, Trudell et al. 1987, Kotagal et al. 2012, Bhatia et al. 2011). The negative effect on neuronal excitability is the main mechanism of action in humans with paroxysmal dyskinesia or episodic ataxia and may also be the main mechanism of action in the puppy of this case report (Kotagal et al. 2012, Bhatia et al. 2011).

Acetazolamide in dogs is mainly used for non-neurological diseases as a diuretic and in glaucoma (Gelatt et al. 1979). Hyperchloremic metabolic acidosis and mild depletion of potassium is described in dogs treated with acetazolamide (Haskins et al. 1981). No abnormalities, however, were seen on repeated blood examinations in this puppy. In human medicine, nephrolithiasis, hyperhidrosis, paresthesia, muscle stiffness and gastrointestinal disturbances are possible adverse effects of acetazolamide (Strupp et al. 2007).

In one report, long-term follow-up of two CKCS with EFS was described (Shelton 2004). At the age of two years, resolution of clinical signs was reported, with the dogs being asymptomatic and no longer requiring medication. Also in dogs with SC, clinical signs decrease in severity with time (Urkasemsin and Olby 2015). One year after starting the treatment with acetazolamide in this puppy, there is still complete remission of the clinical signs and the owners have not reported adverse effects of treatment.

1. References

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Figure captions

Figure 1: Image taken from a video of an episode which lasted for a few seconds. This episode was triggered by playing with another puppy. The hypertonicity disappeared when the other puppy was removed. This video can be seen at https://vimeo.com/143112587 and https://vimeo.com/143112784.

Figure 2: Cryosection from the cranial tibial muscle following the myofibrillar ATPase reaction at pH 9.8. At this pH, type 1 fibers are light staining and type 2 fibers are dark staining. The normal mosaic pattern of muscle fiber types is present. Note that dark staining type 2 fibers are smaller than light staining type 1 fibers (type 2 fiber atrophy).