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CASE REPORT

A Cavalier King Charles dog with shadow chasing: Clinical recovery and normalization of the dopamine transporter binding after clomipramine treatment

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Abstract A 30-month-old female Cavalier King Charles dog was presented with a history of worsening compulsive behavior (shadow chasing). In vivo brain imaging using single-photon emission computed tomography and the dopamine transporter (DAT)-specific radiopharmaceutical ^{123}I-FP-CIT revealed a significantly higher DAT striatal-to-brain ratio. Treatment was started with the tricyclic antidepressant clomipramine 2.5 mg/kg PO, q. 12 hours. After 2 months of medication that resulted in clinical improvement, the DAT binding regained normal values.

Introduction

The expression of excessive, uncontrollable and repetitive motor behavior is a sign common to stereotypic behavior in animals and to obsessive compulsive disorder (OCD) in human beings. The neurocircuitry of OCD is primarily located in the orbitofrontal cortex and the cortico-striatal-thalamic-cortical loops (Stein, 2002; Maia et al., 2008), but other brain areas such as the dorsolateral prefrontal cortex, the anterior cingulate cortex and the amygdala have been included more recently (Friedlander and Desrocher, 2006; Menzies et al., 2008). Both serotonergic and dopaminergic neurotransmitter pathways are known to be involved in OCD (Westenberg et al., 2007). Serotonergic involvement is mainly based on the successful pharmacological treatment of OCD with selective serotonin reuptake inhibitors (e.g., fluoxetine) or the induction of compulsive behavior after administration of serotonin (5-hydroxytryptamine [5-HT]) receptor agonists (Vandebroek and Odberg, 1997; Westenberg et al., 2007). Other clinical and preclinical studies additionally provide evidence that the dopaminergic neurotransmitter system (highly concentrated in the striatum) is involved in the pathophysiology of OCD in human beings and stereotypic behavior in animals (Rapoport and Wise, 1988; Kennes et al., 1988; Pitman, 1989; Denys et al., 2004b).

Evaluating the dopaminergic system is possible by either (1) peripheral measurements (e.g., dopamine metabolite

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homovanillic acid in cerebrospinal fluid or blood), but the results are seldom straightforward because of the uncertain relationship between peripheral and central processes, or (2) central measurements using in vivo functional imaging modalities such as single-photon emission computed tomography (SPECT).

SPECT is a nuclear imaging technique based on the intravenous injection of a gamma ray emitting isotope (mostly ^{99m}Tc or ^{123}I). Detectors on the gamma-SPECT camera rotate around the patient and register these gamma rays. Subsequently, a reconstruction of the acquired data allows cross-sectional slice analysis as well as 3-dimensional view of the patient. Together with the radiopharmaceutical ^{123}I-FP-CIT, which is the combination of (1) the radioactive isotope iodine ^{123}I required for imaging and (2) FP-CIT, a cocaine analogue binding at the dopamine transporter (DAT), SPECT imaging allows evaluating the DAT availability, a biomarker for the dopaminergic neurotransmission (Alvarez-Fischer et al., 2007).

Case description

The present case report describes a drug-naive, 30-month-old, 10-kg intact female Cavalier King Charles dog. The problematic behavior was first noticed at 18 months of age, with sporadic fixating and chasing shadows. It was, however, exclusively noticed on one specific wall on which shadows were created by reflections of the sun. During this behavior, the dog did not respond, as she usually use did, to her name or obeyed to basic requests as "sit" or "down." Repeated signals were necessary to engender compliance. Gradually, additional behaviors, such as excitement and agitation, accompanied by barking, excessive salivation and licking were noticed; these usually started after 2-3 minutes of fixation. The frequency of the behaviors also increased (to maximum of 4 hours a day), along with the level of excitement and agitation. Videotape analysis showed that the behavior also occurred during the absence of the owner. The 3 other dogs in the household did not show any signs of shadow chasing. No abnormalities were noticed on physical, neurological, laboratory, dermatologic, or ophthalmalogic examination. The CBARQ questionnaire (Canine Behavioral Assessment and Research Questionnaire; Hsu and Serpell, 2003) revealed no co-morbid aggression or anxiety. The results of the blood work revealed normal values. The definitive diagnosis of OCD in canines was made on the basis of finding repetitive, stereotypic motor behavior (i.e., shadow chasing) that occurred in a disproportional frequency and duration (Overall and Dunham, 2002; Irimajiri et al., 2009). This case study was approved by the local Ethical Committee of the Faculty of Veterinary Medicine, Ghent University.

In this case study, a brain perfusion scan (with ^{99m}Tc-ECD), a serotonin 2A receptor scan (with ^{123}I-R91150), and a DAT scan (with ^{123}I-FP-CIT) were performed to check for brain abnormalities and possible involvement of the serotonergic or dopaminergic system. These 3 scans were performed under general anesthesia (sedation: intravenous [iv] injection of medetomidine hydrochloride [Domitor; Pfizer] 1,000 μg/m^2 body surface area 30 minutes before the scan; induction: iv propofol [Propovet; Abbott]; general anesthesia: isoflurane [Isoba; Schering-Plough] on oxygen), using a triple-head gamma-camera (Triad, Trionix, Twinsburg, OH) equipped with low-energy ultra-high resolution parallel hole collimators (8-mm spatial resolution).

The dog was scanned weekly for a period of 3 weeks. Acquisition of the perfusion scan was started 30 minutes after 773 MBq ^{99m}Tc-ECD was injected iv and it lasted for 20 minutes. This scan is very valuable because it not only reflects the brain neuronal activity, but it can also rule out anatomical brain abnormalities (e.g., hydrocephalus) that may be implicated in OCD. Additionally, scans can be used as anatomical map to evaluate the 5-HT2A receptors scans.

For evaluating the serotonergic neurotransmitter system, the SPECT tracer ^{123}I-R91150 (with high affinity and selectivity for the 5-HT2A receptor, which is involved in impulsivity and anxiety) was injected (dose, 133 MBq) 90 minutes before the acquisition (30 minutes). Using a region-of-interest analysis, it was feasible to calculate the 5-HT2A receptor availability in the frontal, temporal, parietal, and occipital cortex, as well as in the subcortical region, a detailed description of which is found in the study by Peremans et al. (2003).

Finally, evaluation of the dopaminergic neurotransmission was achieved by means of an iv injection of the highly selective DAT tracer 123I-FP-CIT (dose, 116 MBq), 3.5 hours before the acquisition (30 minutes). Values were compared with the previously calculated normal canine values based on the resolution-independent method of Dobbeleir et al. (Vermeire et al., 2010). In short, regions of interest were drawn over the left and right striatum (S) and over a third region, thus covering almost the whole brain. The calculations were done on the basis of the following formula (Dobbeleir et al., 2005):

$$\text{Striatal to brain uptake ratio} = \frac{\text{counts in } S - \left(\text{counts in BG} \times \frac{\text{cm}^3 \text{ in } S}{\text{cm}^3 \text{ in BG}}\right)}{\frac{\text{counts in BG}}{\text{cm}^3 \text{ in BG}}}$$

With

$$\text{counts in background (BG)} = \text{counts in brain ROI} - \text{counts in striatal ROIs}$$

and S = striatum.

No brain perfusion or serotonin 2A receptor abnormalities were noticed. In contrast, the DAT scan revealed significantly higher DAT ratios in left (= 25.98; normal value: 15.39 ± 2.38 [mean ± SD]) and right (= 26.14; normal value: 15.23 ± 2.23 [mean ± SD]) striatum.

Treatment was started with clomipramine, a tricyclic agent with both antidepressant and antiobsessional properties blocking the neuronal reuptake of serotonin and