Retrospective study on hypersensitivity-hyperactivity syndrome in dogs: long-term outcome of high dose fluoxetine treatment and proposal of a clinical score

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Abstract: In the French veterinary psychiatry model, the canine version of attention deficit hyperactivity disorder is called Hypersensitivity-Hyperactivity Syndrome (HSHA) and it includes two stages, depending on the symptom severity. Since methylphenidate is not authorized for veterinary use in France, HSHA dogs are commonly treated with 2 to 4 mg/kg Fluoxetine associated with behavioral modifications. Thus, the aim of this study was to analyze the long-term outcome of this approach. Twenty-four dogs diagnosed with HSHA were included. For each dog, 42 descriptive data were analyzed. Primary reasons for consulting were variable if the dogs had an additional behavioral diagnosis (i.e. 33% of the dogs): complaints were linked to the comorbid diagnosis (e.g. bite on strangers, people phobia), whereas they were linked to autocontrol deficiency for the dogs diagnosed with HSHA only (e.g. destructive, mouth, jumps on people). HSHA affection deeply alters the dog-human bond, as severe cases often lead owners to think about euthanasia or rehoming (12% for stage 1, but 83% for stage 2).

Neither the possibility to have access to a garden nor the quantity of daily exercise were linked to HSHA stages (respectively, fisher's exact test, p=0.69, and Kruskal-Wallis, p=0.88).

Eighty-three percent of the dogs attended training classes before consulting, with no noticeable improvement (mean training improvement score 1.7/10). In addition, training seemed even less efficient on severe cases, i.e. stage 2 dogs (Kruskall-Wallis, p<0.03).

After two months of high dose Fluoxetine (2 to 4 mg/kg), the average score of improvement given by owners was 7.2/10 compared to 0/10 at start. No long-term adverse effect was reported.

A HSHA clinical score (0 to 5 scale) was built to better categorize the dogs and to conduct the follow-up. The HSHA clinical score was correlated to Fluoxetine dose (Pearson correlation, p<0.01) and duration (Pearson correlation, p<0.05). A successful weaning from treatment was possible for 54% of the dogs.

These results suggest that HSHA spectrum can range from mild clinical signs to widely pervasive and invalidating ones. Starting the treatment as early as possible seems determinant for the welfare of the dog and for the dog-owner relationship, but doesn't allow a shorter treatment (Kruskall-Wallis, p=0.84) or more chances for a weaning (Fisher's exact test, p=0.88). However, high dose Fluoxetine associated with behavioral modifications appear to be useful and well tolerated to treat this complex syndrome.

Key Words: dog; hyperactivity; impulsivity; hypersensitivity; hyperreactivity; fluoxetine; ADHD-like syndrome.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized in humans by pervasive and impairing symptoms of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2017). It is one of the most thoroughly researched disorders in human medicine, with a worldwide prevalence going from 8-12% (Faraone et al., 2003) up to 20% depending on the studies (Polanczyk et al., 2007). This neurodevelopmental disorder has been associated to many negative outcomes for the patients and a financial burden for families and society (NIH consensus statement, 2000).

In the veterinary field, many names can be found embracing the concept of impulsive, rest-

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less and inattentive dogs like overactivity, hyperactivity/hyperkinesis, hyperreactivity (Overall, 2013), hypermotricity (Landsberg et al., 1997), impulsivity (Wright et al., 2012), hypersensitivity-hyperactivity syndrome (HSHA) (Pageat, 1998).

In the last decade, two owner-based questionnaires have been built in order to measure attention skills and activity/impulsivity in pet dogs (Vas et al., 2007; Wright et al., 2011). Recently, more evidence has been reported to support the idea that dog might be a spontaneous model of ADHD (Lit et al., 2010; Puurunen et al., 2016). However, the limit between normal and pathological levels of impulsivity in dogs remains undefined.

Since methylphenidate was the first-choice treatment for ADHD in humans, research focused on dopamine receptors. However, it also has been established that psychostimulant primary calming effect in dopamine transporter knock-out mice was mediated by the serotoninergic system (Gainetdinov et al., 1999). More results using rodent models provided strong evidence to support the importance of serotonin in behavioural persistence and impulse control (Fonseca et al., 2015). Recently, glutamate (Isherwood et al., 2017; Miller, 2014) and GABA (Boy et al., 2011) have also been reported to play some role, illustrating the complexity of ADHD pathophysiology and indicating that many neurotransmitters are involved. In humans, the picture emerging from studies of dopamine, serotonin and impulsivity, is that different types of impulsivity appear to be modulated differentially by the different monoamines (Dalley & Roiser, 2012). Finally, despite the fact that the majority of research has focused on the role of dopamine in impulsivity over the past decade, a return to serotonin seems warranted. In particular, it will be important to characterize further the nature of interactions between dopamine and serotonin in influencing different types of impulsivity (Dalley & Roiser, 2012; Oades, 2007).

In dogs, genetic research focused on the canine dopamine receptor D4 (Ito et al., 2004) and suggested its association with activity-impulsivity endophenotype (Hejjas et al., 2007). Methylphenidate has been reported as a possible treatment of HSHA for dogs too (Piturru, 2014), but this drug is not available in France for veterinarians. Hence, the most common medication used by French veterinarians to treat HSHA syndrome is fluoxetine at a dose of 2-4 mg/kg per day (Beata, 2017; Marlois et al., 2017). This dosage is higher than the usual use of fluoxetine at 1 to 2 mg/kg, but it has been established by experience of veterinary behaviorist over 20 years of practice (Mege et al., 2003). Such treatment has been also supported by several studies in humans (Barrickman et al., 1991; Carlisi et al., 2016; Chantiluke et al., 2015) without adverse effects, even on patients with epilepsy (Kanner, 2016). In dogs, Fluoxetine has been used for long in behavioural medicine (Dodman et al., 1996; Wynchank & Berk, 1998) in other indications, and always at lower doses ranging from 0.1 to 2 mg/kg (Denenberg 2015; Dodman et al., 1996; Ibáñez & Anzola, 2009; Irimajiri et al., 2009; Pineda et al., 2014; Simpson et al., 2007; Wynchank & Berk, 1998). One recent case report concerned HSHA, but the dose was around 1 mg/kg per day (Luno et al., 2015).

Therefore, the main purpose of this study was to assess the efficiency of a treatment of Fluoxetine at 2-4 mg/kg combined to behavioral modification on HSHA dogs. Secondly, as the clinical pattern of this syndrome is very rich and complex, we aimed to propose a clinical scoring system based on categories of clinical signs that could be helpful for veterinarians to resume the severity of the HSHA syndrome and to propose a prognosis.

Materials and methods

Case selection

Computer data files from the first author practice were extracted for records of dogs with a diagnosis of HSHA (using Mege and colleagues' criteria (2003)) that were examined for the first

time between 1st January 2016 and 31th December 2016. This selection resulted in 28 cases with a HSHA diagnosis (among a total of 75 cases referred for behavior consultation). Four cases were excluded from the current study because 2 dogs were given another treatment than Fluoxetine, and 2 owners refused to give any medication to their dogs.

Finally, 24 dogs were included in the study and all of them attended one or several follow up consultations between 11th March 2016 and 31th December 2017.

Behavior consultations

As shown in Figure 1, each dog included in the study attended an initial consultation of 90 min. It included the review of the history form completed at the arrival of the owner in the practice, discussion of behavioral issues and main complaints, detailed description of each behavior, direct observation of the dog and physical examination. Each consultation was conducted by a veterinary behaviorist (i.e. first author).

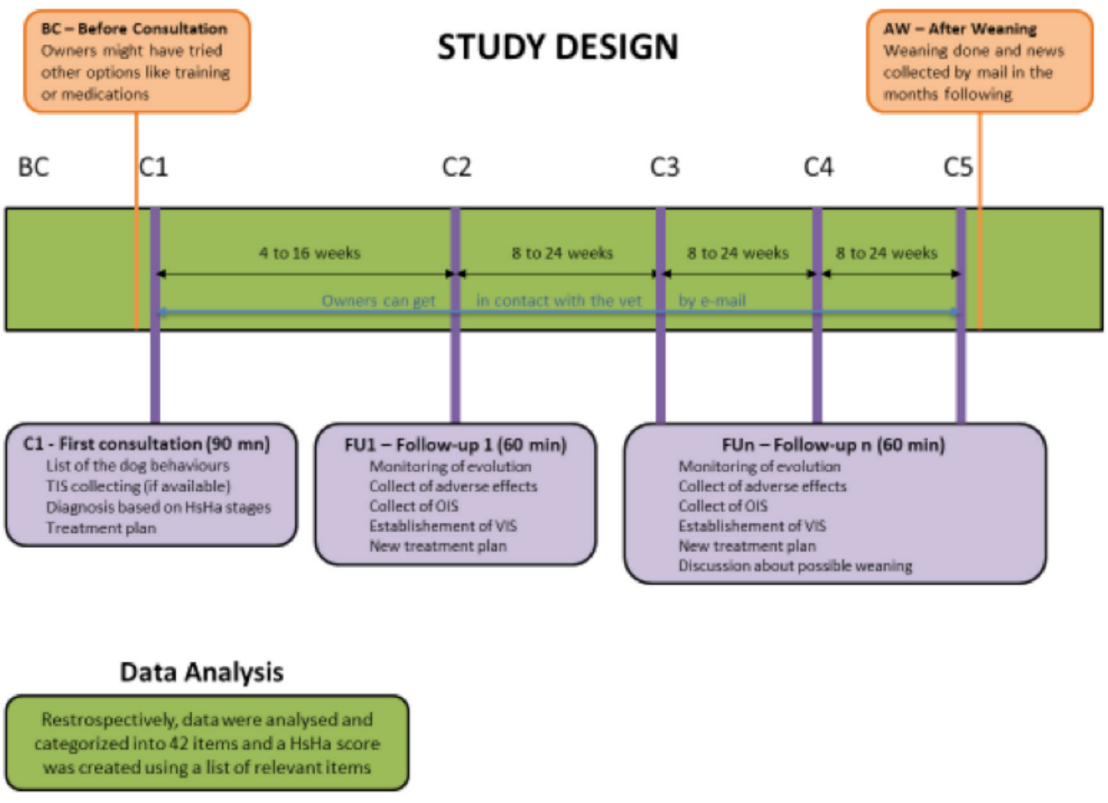

Figure 1. Study design.

HSHA diagnoses were established using Mege and colleague's definition of the HSHA syndrome (Mege et al., 2003). The two HSHA stages initially defined by Pageat (Pageat, 1998) were slightly modified by adding an intermediate stage for dogs fitting only one of the two criteria (no food satiety or hyposomnia) of the stage 2. This intermediate stage was called stage 1.5 (Table 1).

Table 1. Criteria used to diagnose and categorize HSHA.

HSHA stage	Diagnosis criteria
1	Non-acquisition of bite inhibition after 2 months of age Hypermotricity: incapacity to stop a behavior after the consumer phase, on the contrary, re-appearance of a new appetitive phase Hypersensitivity: reaction to stimuli that are permanently present in the environment Normal food satiety and sleeping behavior
1.5	Stage 1 criteria Lack of food satiety OR hyposomnia: under 8 hours of sleep per 24 hours
2	Stage 1 criteria Lack of food satiety Hyposomnia: under 8 hours of sleep per 24 hours

A suitable treatment plan was developed for each dog including medication and environmental and behavioral modifications. In order to ensure humane and non-aversive care, qualified trainers addresses were given to owners to follow the training plan. Concerning medication, an initial Fluoxetine dose was prescribed.

Considering the dosages prescribed, all the owners were clearly informed about the possible adverse effects that they could observe during the first ten days of treatment and the first author was available by mail if they had questions about it. In addition, after information, they were given the choice to accept the medication or not. If adverse effects (AEs) were reported by owners, the dose was adjusted until the AEs resolve. The doses reported in the study are the adjusted ones, which were kept for the duration of the treatment: they are the lowest efficacious doses. Fluoxetine doses were also adjusted during the follow up consultations to keep the dosage per dog's weight constant.

A follow-up consultation was planned between one and four months after the first one, depending on the severity of the case and the need for a close monitoring. However, medication was always prescribed for a maximum of 6 months, to allow a re-examination of the dogs under treatment. Medical records of the dogs were obtained when needed from the referring veterinarians. When drug prescription exceeded 6 months, biochemical analyses were asked (ALP, ALT, glucose, total protein, creatinine, and urea) in order to assess the liver function. All 24 cases attended at least one follow-up consultation to monitor the case evolution, which included self-reported owner compliance, recording of side-effects, dog improvement scale (owner based), monitoring of the problematic behaviors and direct observation. In addition, owners could contact the veterinarian by e-mail between appointments if they wanted to.

Data collection

Data collected from case records included dog signalment and history, clinician observations, recommendations and prescription. Descriptive data recorded included name, age, breed, sex, weight and neuter status of each dog. During the consultation, owners provided information by responding to open-ended questions. This included adoption history, systematic behavior work up (eating, drinking, sleeping, playing, exploring, agonistic, housetraining, somatosensory, phobias, sexual), attachment evaluation, previous training history and methods, living conditions (garden access, daily exercise: type and length). One close ended-question was asked to assess the emergency of the situation, asking the owners if they were thinking about euthanasia or re-homing of their dog.

The retrospective aspect of the study led the authors to choose a limited number of items that would be available from most the reports and that seemed relevant for HSHA assessment. This

resulted in 42 items that were filled up for each dog to conduct the data analysis (Table 2).

Table 2. List of the items used to analyze the data.

Item Category	Item list	N°
Descriptive data	Date of the first consultation	1
	Owner name	2
	Dog name	3
	Dog breed	4
	Age of the dog when first consultation occurred	5
	Age class: puppy, puberty, adult	6
	Dog sex: male, neutered male, female, neutered female	7
	Dog weight	8
Diagnoses	Nosographic diagnosis: HSHA1, HSHA1.5, HSHA2	9
	Comorbid behavioural diagnosis	10
Follow-up	Number of follow-up consultations	11
Presenting complaint	Presenting complaint	12
	Did you ever think about euthanasia or rehoming? yes, no	13
Medical treatment	Name of the prescribed drug	14
	Dose in mg per day	15
	Dose in mg/kg	16
	Side effects reported	17
	Additional drug prescription	18
	Treatment duration before weaning	19
Adoption context	Development conditions before adoption	20
	Age of adoption	21
Autocontrol items	Age of acquired bite inhibition	22
	Oral exploration of non-edible items after 6 months of age	23
	Ingestion of non-edible items: yes, no	24
	Hypersensitivity (i.e. too low trigger threshold): yes, no	25
	Hyper-reactivity (too high intensity): yes, no	26
	Self-stopping capacity when no stimulation: yes no	27
	Tachycardia, tachypnea: yes, no	28
	Food satiety: normal, no satiety	29
	Sleep duration in hours	30
	Exploration description: as example messy, mouthing, in height,..	31
	Play description: as example brutal, never stops, mouth,…	32
Agonistic behavior	Aggression type	33
Environment factors	Other adult dog present in the house: yes, no	34
	Length of daily exercise outside the dog home in minutes per day	35
	Access to a garden	36
Training	Length of education before consultation in months	37
	Training method: aversive, non-aversive, both, unknown	38
	Training Improvement Score (TIS)	39
Improvement	Owner Improvement Score (OIS): -10 to +10 scale	40
	Veterinary Improvement Score (VIS): -10 to +10 scale	41
Weaning	Reason for no weaning	42

For the owners who followed training classes before the consultation, an assessment of the training efficacy regarding the presenting complaint was recorded during the initial consultation, ranging from -10 (the dog behavior worsened dramatically) to +10 (the dog behavior improved dramatically) and ranking the dog at 0 when training started. This score, filled with the owner during the consultation 1, was called Training Improvement Score (TIS).

During the follow-up consultations, all undesirable or abnormal behaviors were rechecked with the owners to monitor the clinical improvement. An Owner Improvement Score (OIS) of the dog was filled with the owners, using a -10 (dog behavior has worsened dramatically) to +

10 (dog behavior improved dramatically) scale, considering that the dog started with a 0 score at the first appointment.

The practitioner also scored the dog improvements based on the symptoms collected, using a similar scale ranging from -10 (symptoms worsened dramatically) to +10 (symptoms improved dramatically). We called it Veterinarian Improvement Score (VIS). OIS directly testifies the owner satisfaction, whereas VIS is rather reflecting the dogs' clinical improvement.

However, OIS and VIS were not always collected at a similar rhythm from one case to another because the length between appointments could vary amongst dogs. Hence a choice was made by the authors to choose the latest OIS and VIS collected to conduct the analysis from baseline in order to have a long-term picture of the global trend. Nevertheless, the authors checked that OIS and VIS scores were always equal or better than the previous one.

Relevant HSHA items and HSHA clinical score

Several items were chosen to conduct the statistical analysis because they seemed relevant regarding HSHA syndrome (Table 3a).

Table 3a. Definition of items used to establish the HSHA clinical score.

List of the selected items used to calculate HSHA score	**Definition**
Bite inhibition	Capacity of the dog to control his bite when excited, resulting in the total absence of wounds on the human skin during play sessions
Oral exploration after 6 months	Chewing and destruction of non-edible items after the age of 6 months
Non-edible item ingestion	Ingestion of non-edible items including plastic, stones, wood, fabric, toys
Hypersensitivity	Too low reactivity threshold. Example: the dog will react to stimulus that shouldn't make him react, like low sounds, or movements, or unmoving items.
Hyper-reactivity	Too high intensity of the dog reaction. Example: the dog will overreact when playing, greeting people
Spontaneous stopping capacity	Capacity of the dog to stop moving and rest when no stimulation is around him, without being told to do so. Example: without stimulations (sound or movement) when he is home a dog without stopping capacity will never settle if not told to do so
Tachycardia-Tachypnea	Tachypnea: respiratory rhythm over 40 per minute Tachycardia: Cardiac rhythm over 120 per minute (large dogs) or 160 (puppies and small dogs)
Lack of food satiety	Inability of the dog to stop eating even after his physiological needs are reached. Owners will report very fast ingestion, food stealing, capacity to eat a meal twice in a raw, brutality when taking food from hands, high motivation around food
Hyposomnia	Sleeping time under 8 hours a day
Abnormal game	Were considered abnormal games the following items (reported by owners and under direct observation): Brutality: the dog can hurt people while playing (runs into them, pushes them, … Incapacity to give item back Endless play while the partner plays Endless play alone: as long as a toy is present the dog will play obsessively

Abnormal exploration	The following items were considered abnormal exploration under direct observation of the dog in a new environment: Messy: zapping from one item to another without finishing any exploration sequence Jumping: the dog jumps to explore what is on tables Endless: the dog never stopped to move for 90 minutes Oral: the dog grabs items in the consultation
Aggression	Any form of aggression (growl or bite) was collected, including Play aggression Pain aggression Fear aggression Food-related aggression Possessive: to protect an item Protective: to protect a person Inter-dog aggression Territorial aggression

A HSHA clinical score was created to get a quantitative value of the severity of the clinical picture (Table 3b), and to assess the reliability of this score with the duration of the treatment or the possibility of successful weaning.

Table 3b. Values used to establish HSHA score.

Score Name	**Scale used for scoring**	
Bite Inhibition	0	Acquired at 2 months
	1	Acquired at 4 months
	3	Acquired at 6 months
	5	Acquired after 6 months (or never)
Oral exploration	0	No oral exploration after 6 months old
	1	Can shred non-edible objects occasionally
	3	Shred non-edible objects regularly and/or a lot of different types
	5	Ingestion of non-edible objects
Reactivity	Each of the five item is scored 0 or 1 (presence/absence) and added up for a 0 to 5 score: hypersensistivity, hyperreactivity, spontaneous stopping capacity, Tachycardia-tachypnea, lack of food satiety	
Sleeping	0	> 10 hours
	1	> 8 to 10 hours
	3	> 7 to 8 hours
	5	< 7 hours
Playing	0	Able to play without brutality and respecting the partner rules
	1	Brutal and won't give back toys
	3	Endless play as long as the dog has a partner
	5	Obsessive play as long as a toy is available
Aggression	0	No aggression
	1	Only play aggression
	3	Other aggressions than during play appearing after puberty
	5	Other aggressions than play exhibited very early before puberty

This score calculation was based on the quantitative evaluation of 6 clinical items ranging from 0 to 5 (Table 3a&b). It was calculated using the average of the 6 items. Five items of the score were clinical items directly available during behavior consultation, and one – age of acquisition of bite inhibition – was only available through the owner report. For adopted dogs for which this item was missing, the clinical score was the average of 5 items instead of 6.

Statistical analysis

Because it was assumed that the data could not be normally distributed, non-parametric statistical tests were preferred to analyze the data, including Pearson Chi-squared tests, Fisher's exact tests, and Kruskall-Wallis for qualitative data, Wilcoxon signed rank tests and Mann-Whitney for quantitative data. For each record, 42 pieces of descriptive data were entered for analysis. Results of the tests were obtained using R statistical software (https://www.r-project.org).

A p value of < 0.05 was chosen as threshold for statistical significance.

Results

Dogs characteristics

The study involved 14 males (58%) and 10 females (42%). Fifty three percent of the males (n=6) and 20% of the females (n=2) were neutered. Dogs weighted 7 to 53 kg (average 22.1 kg). Their age ranged from 4 months old to 60 months old at the time of the initial consultation (mean 14.2 months).

According to the owner's descriptions and to direct observations, the 24 dogs were grouped according to FCI (Fédération Cynologique Internationale). Six out of the nine groups were represented in the study as follows: sheep dogs and cattle dogs (n=11), molossoid (n=1), terrier (n=4), pointing dogs (n=2), retrievers (n=4), companion and toy dogs (n=2). Eleven dogs were purebred (46%), seven were of breeds not recognized by the FCI (29%) and six were of mixed breeds (25%).

One dog had concomitant pathological conditions (chronic otitis and atopic dermatitis). An encephalic scan was asked for another of the dog because his response to medication was inconsistent and the examination revealed hydrocephalia explaining the erratic outcome.

The number of follow-up appointments ranged from 1 to 4 as follow: six dogs (4/24 [17%]) attended one follow-up consultation, eight dogs (8/24 [33%]) attended two, nine dogs (9/24 [37%]) attended three and three dogs (3/24 [13%]) attended four.

Reasons for consulting and associated diagnoses

To analyze the reasons for consulting, dogs were divided into two groups: dogs diagnosed only with HSHA (HSHA only group) and dogs diagnosed with a comorbid behavioural diagnosis (HSHA+ group). HSHA only group consisted of 16 dogs (67%, N=16/24), including 5 adults, 5 teenagers and 6 puppies, whereas HSHA+ group consisted of 8 dogs (33%, N=8/24), 3 adults and 5 teenagers. The age of the dog at the first appointment was 13.8 months average for the HSHA only dogs and 14.8 months average for the HSHA+ group. The comorbid diagnoses included communication trouble (17%, N=4/24), sociopathy (8%, N=2/24), deprivation syndrome (8%, N=2/24).

However, their distribution is different depending on the HSHA stage: in HSHA stage 2 dogs, the only comorbid diagnosis was communication trouble, whereas in dogs with lower stages, other comorbidity diseases were diagnosed.

Our results show that the reasons for consulting were different in both groups like illustrated

by Figure 2: complaints in HSHA only group were linked to autocontrol deficiency signs (e.g. destructive, grabs or mouth, jumps on people, …), whereas complaints in HSHA+ group were more often signs linked to comorbid diagnosis (e.g. bite on strangers, people phobia).

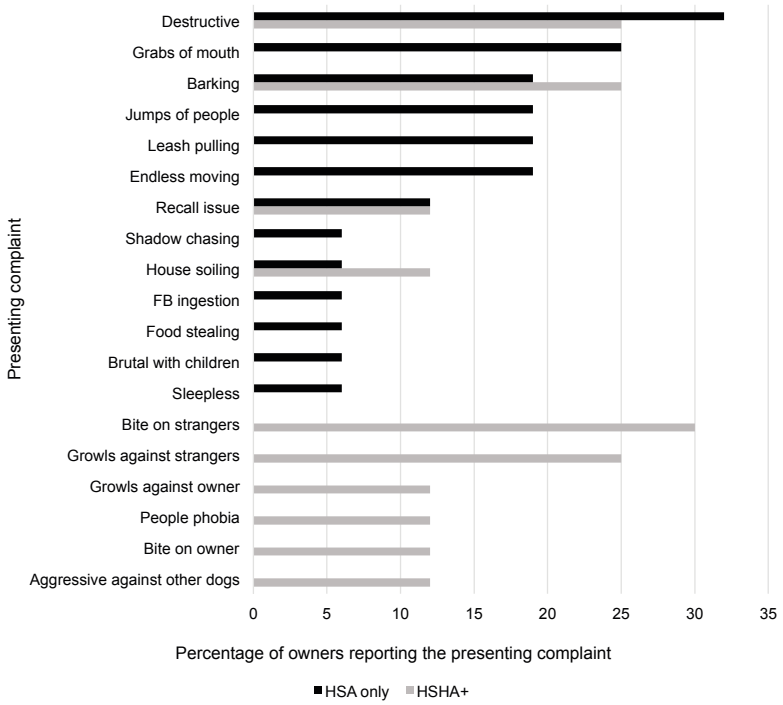

Figure 2. Comparison of the owner's reasons driving to consultation between HSHA only dogs and HSHA+ dogs.

Link with euthanasia or rehoming

Fifty-four percent of the owners (n=13) answered that they were thinking about euthanasia or rehoming/relinquishment of their dog during the first consultation. Such solution was considered by 12% (N=1/8) of the owners of dogs with a stage 1 diagnosis, compared to 50% (N= 2/4) for stage 1.5, and 83% (N=10/12) for stage 2 (Fisher's exact test, $p < 0.01$).

Age of acquisition of bite inhibition appears to be another at risk factor: when inhibition was not acquired after 4 months, 58% owners (N=7/12) thought about euthanasia or rehoming, whereas only 28% (N=2/7) thought about it when bite inhibition was already acquired at 4 months, but Fisher's exact test gave a non-significant result ($p = 0.34$). For 5 dogs the information was not available because they were adopted adult and all of their owners (N=5/5) were thinking about euthanasia or rehoming.

Sleeping duration appears as a determinant cofactor in euthanasia or rehoming decision. Normal sleep duration was indeed recently evaluated around 12 to 16 hours, with variations depending on age and feeding frequency (Zanghi et al., 2013). 83% (N=10/12) of owners of dogs sleeping less 8 hours thought to euthanasia or rehoming compared to 25% (N=3/12) of owners with dogs sleeping more than eight hours (Fisher's exact test; $p < 0.02$).

Out of the 24 dogs included in this study, no one got euthanized or abandoned up to the time this article has been written. One of the dog diagnosed with HSHA stage 2 and hydrocephalia died later during a surgery (enterectomy performed after foreign body ingestion).

Training methods and physiological needs prior to the first consultation

19/24 (79%) dogs had access to a garden and 17/24 (71%) were walked daily (75 min of mean

walking in stage 1 dogs, 52 min for stage 1.5 and 64 min for stage 2), and these opportunities to do physical exercise were not linked to HSHA stages (respectively, Fisher's exact test, p=0.69, and Kruskal-Wallis, p=0.88).

Out of the 24 dogs, 83% (N=20/24) attended training classes. The length of the training ranged from 1 to 12 months prior to the first behaviour consultation. Thirty percent (N=6/20) described aversive training methods, while the other 70% described non-aversive ones. Aversive training methods were not more significantly used with dogs presenting comorbidity, than with dogs presenting HSHA only (Fisher's exact test, p =0.12). Duration of attendance to training classes (4 months for stage 1 dogs, 5.5 months for stage 1.5 dogs and 4.6 months for stage 2 dogs) was not linked to HSHA stage (Kruskal-Wallis, p=0.41).

The average TIS reported was 1.7. No significant difference was found concerning TIS between aversive training group (arithmetic mean TIS = 2) and reward-based training group (mean TIS = 1.5) (Kruskal-Wallis,p=0.36). In addition, HSHA2 dogs have significant less improvement with training than other dogs (Kruskall-Wallis, p<0.03).

Medication choice, doses and adverse effects

The 24 dogs were all treated with Fluoxetine. Among them, 12.5% started with another medication (Clomipramine or Selegiline) but they finally received Fluoxetine at a dose ranging from 2.2 to 4.4 mg/kg single in day (Figure 3).

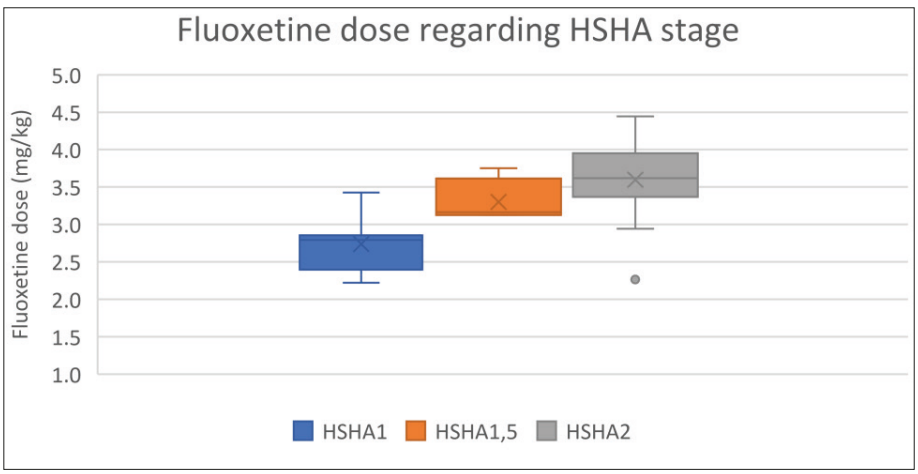

Figure 3. Fluoxetine administered dose versus HSHA stage.

A higher dose of Fluoxetine was needed to stabilize dogs behavior when the HSHA stage was more severe, with a mean dose of 2.8 mg/kg in HSHA stage 1 compared to 3.2 mg/kg for stage 1.5 dogs and 3.6 mg/kg for stage 2 dogs (Kruskal-Wallis; p<0.01,). Fluoxetine dose correlated with HSHA score (Pearson correlation, p<0.01). For two dogs, administration of Cyproterone acetate at 2 mg/kg twice a day was added afterwards, because Fluoxetine alone was not sufficient to control the exhibited symptoms.

Concerning AEs, each owner was explained, during the first consultation, the possible adverse effects expected especially during the two first weeks of treatment: decrease in appetite and lethargy. 29% of owners reported side effects during the first follow-up consultation, including appetite decrease (N=4/24), shaking (N=3/24), lethargy (N=1/24). The doses were adjusted for 2 dogs (going from 2.6 to 2.3 mg/kg and from 3.5 to 3.2 mg/kg for the other dog), because of the AEs reported. No other side effect was reported afterwards.

Concerning the blood controls asked to the owners when the treatment duration exceeded 6 months (N=17/24), not all the owners agreed to do them, especially because the dogs exhibited no side effects. However, 12 out of 17 reported the results of the blood tests and none was outside of the normal range (ALP, ALT, glucose, total protein, creatinine, and urea).

Improvement assessment

Improvement was assessed subjectively through the two scores performed by the owner, i.e. TIS and OIS, and by the veterinarians with the VIS (Figure 4).

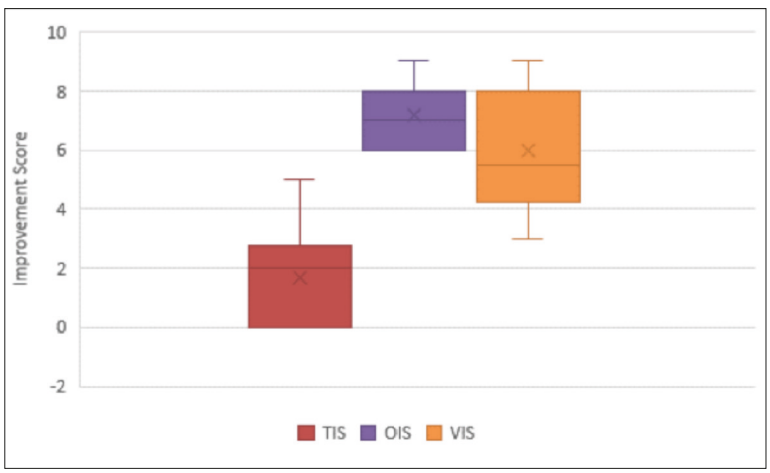

Figure 4. TIS, OIS and VIS Improvement Scores.

According to owners, dog improvement was significantly higher after a high dose Fluoxetine treatment combined with behavioral modification (mean OIS=7.2) compared to training alone (mean TIS=1.7) (Mann-Whitney U test; $p<0.01$).

The owners seem more positive in assessing their dogs than the veterinarian with OIS score being significantly higher than VIS, with mean values of respectively 7.2/10 for OIS and 6/10 for VIS (Kruskall-Wallis: $p<0.03$). The OIS and VIS were not significantly different according to HSHA stages.

Medication duration

A rule was consistently applied by the practitioner: a therapeutic weaning would be encouraged if the improvement score provided by owners was 6/10 for at least four months.

To analyze the data for treatment duration, statistic tests were done considering that the treatment ended on 31th December 2017 (i.e. when the data collecting ended). The Fluoxetine treatment duration ranged from 3 to a minimum of 24 months (study end). When comparing the treatment duration to HSHA stage, it appeared that the higher the HSHA stage was, the longer the treatment was, with a mean of 8 months for stage 1 dogs, 13 months for stage 1.5 dogs and 17 months for stage 2 dogs (Kruskall-Wallis, $p< 0.03$).

As several dogs were still under treatment at the end of the study, the relation between HSHA stage and duration should be even more significant.

Finally, the starting age of the treatment was not linked to the treatment duration (Kruskall-Wallis, $p=0.84$).

HSHA clinical score

The HSHA clinical score was significantly correlated with the HSHA stage diagnosed during the consultation (Kruskall-Wallis, $p<0.01$) (Figure 5).

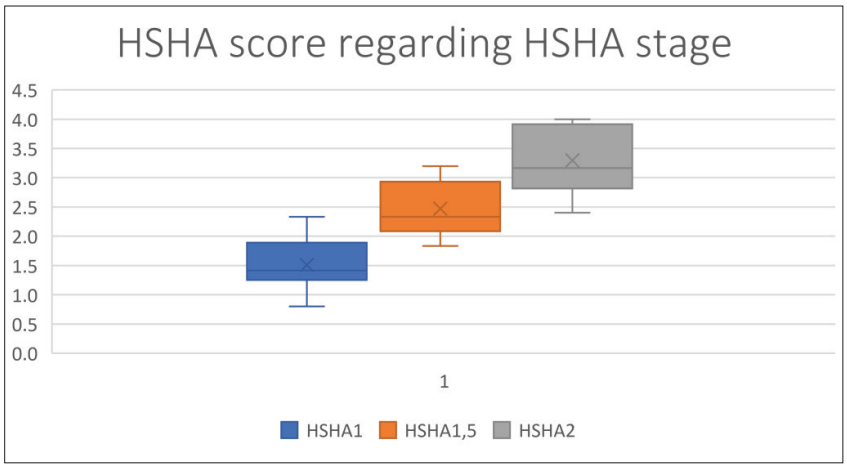

Figure 5. Relation between HSHA score and HSHA stage.

The HSHA clinical score was correlated to Fluoxetine dose (Pearson correlation, $p<0.01$) and duration (Pearson correlation, $p<0.05$). As several dogs were still under treatment at the end of the study, the relation between HSHA clinical score and duration should be even more significant.

Therapeutic weaning

Therapeutic weaning was successfully possible for 54% (N=13/24) of the dogs; respectively 100% of the HSHA stage 1 dogs (N=8/8), 75% of the HSHA stage 1.5 dogs (N=3/4), and 17% of the HSHA stage 2 dogs (N=2/12). Thus, weaning was significantly linked to HSHA stage (Chi^2, $p < 0.01$). But weaning was not linked to the age when the treatment was initiated (Fisher' exact test: $p=0.88$).

For the 11 remaining dogs, weaning either failed (N=3/11) or was not tried (N=8/11). The reasons of the weaning failure (or no weaning attempt) were the same and included reappearance (or still presence) of the following clinical signs: lack of food-satiety, destructive behavior, mouthing, hypersensitivity, aggression, impulsivity. For those dogs, OIS and VIS mean scores were respectively 6.6/10 and 5.6/10 after 12 to 24 months of Fluoxetine treatment, with a mean dose at 3.7 mg/kg. For those 11 dogs, a lifelong treatment was discussed and decided with the owners, as long as the treatment was well tolerated, which was assessed by doing regular biochemistry analysis to monitor long-term liver effect.

Discussion

The authors are aware of the fact that the doses used in this study are higher than the one recommended by the National Agency of Veterinary Medication (ANMV), which is 1-2 mg/kg. In addition, and to the author's knowledge, there is no wide peer-reviewed publication reporting the use of Fluoxetine at such dosage. However, in France, the 2-4 mg/kg dose is considered as a standard by veterinary behaviorist, based on over 20 years of experience. It has been indicated in several continuing education papers and books: in 2003, a national behavior handbook was edited by sev-

eral veterinary behaviorist amongst whom two diplomats from the ECAWBM. The use of 2-4 mg/kg fluoxetine for dogs diagnosed with HSHA syndrome, especially stage 2 is indicated. (Mege et al., 2003). In "Behavior Problem of the dog and cat, 3rd edition" G. Landsberg reported the use of such dosage of Fluoxetine as "reported dose range", which designs known practices without published references (Landsberg, 2013). Numerous shorter French continuing education reports state the use of such dose without adverse consequences (Beata, 2007; Dramard 2007; Marlois et al., 2013; Marlois, 2013). In the future, more standardized clinical studies are required in order to confirm the need of such 2-4 mg/kg dosage for the treatment of HSHA diagnosed dogs.

Despite the youth of the dogs in the study (mean 14.2 months), a high proportion of owners (54%) were thinking about abandon or euthanasia when the first consultation occurred. These results underscore how pervasive and invalidating this neurodevelopmental disorder can be. Moreover, all the re-adopted dogs (i.e. from a shelter or from a first family) of the study were at risk for a new abandon, suggesting that HSHA could have been the initial cause of the abandon. This corroborates previous results acknowledging the primary role of behaviour problems in euthanasia and rehoming (Marston et al., 2004).

Thirty-three percent of dogs diagnosed with HSHA had an ancillary behavioral diagnosis, which confirms an important risk of comorbidity like in human ADHD (Barrickman et al., 1991; Chantiluke et al., 2015).

In stage 2 group, the only comorbid diagnosis identified in our study was communication trouble. It could be due to the small size of the sample, but also to the fact that the disorder is so invading and challenging to live with, that owners punish them sooner, resulting in anxiety and aggressions (Ziv, 2017). The HSHA symptoms might also be so pervasive that it could hide other milder symptoms.

Taken together, these results suggest that this disorder needs to be diagnosed and taken in charge as early as possible (i.e. through behavioral work-up during routine appointments), before owners get so overwhelmed that the dog-human bond is altered (e.g. before euthanasia or rehoming becomes an option).

Another important result comes from the fact that training alone was not efficient to decrease the symptoms, especially in the case of dogs exhibiting a high HSHA score, as demonstrated by the significant difference between TIS and OIS. Access to a garden or tries to calm the dog by increasing daily exercise was not significant either. After the first consultation, some of the owners kept the same training methods while others changed, but all the dogs improved, which suggests that Fluoxetine treatment was a key in the improvement witnessed.

Regarding the two dogs that were excluded from the study at inclusion because they refused the treatment plan, especially the medication, they were contacted a year after the initial consultation to ask if the HSHA conditions had changed and they did not.

All together, these results confirm what has been demonstrated in humans: patients with ADHD do have a brain disorder which is not only a label for difficult children/dogs or caused by incompetent parenting/training (Hoogman et al., 2017), but a long-lasting disease needing behavioral care and medication.

Treatment efficacy was evaluated using owner (TIS and OIS) and veterinary scores (VIS). The significant results obtained, for both OIS and VIS, support the idea that 2 to 4 mg/kg Fluoxetine combined to behavior modification plan was efficient to control HSHA in dogs. OIS and VIS showed close mean even if VIS was slightly lower. OIS directly testifies the owner satisfaction, whereas VIS is more reflecting the dogs' clinical improvement. No matter how subjective these scores can be, the high proportion of owners willing to abandon their dog before treatment compared to the long-term outcome (no euthanasia or abandon, OIS> 7/10 with half dogs weaned) is a solid demonstration of the restoration of the dog-human bond and a better quality of life.

The reported adverse effects (29% of owners) could be under evaluated (especially the mild and transient ones) considering that owners were explained what could be expected. However,

owners did not report new adverse effects with 2 to 4 mg/kg dose compared to those usually reported at 1 to 2 mg/kg (i.e. decreased appetite and lethargy) (Irimajiri et al., 2009; Simpson et al., 2007), and not for longer durations (i.e. resolving under 10 days). No weaning or break in the medication was done for adverse effects reasons, which suggests that Fluoxetine at a dose of 2 to 4 mg/kg seems well tolerated even for long durations (i.e. up to 24 months in the study).

Fluoxetine dose and duration were correlated to the clinical HSHA clinical score, but not to the dog age, which suggests that treating the dog earlier will not allow an earlier weaning. This concurs with recent results of Hoogman and colleagues who demonstrated that volume differences in the brain between ADHD and healthy individuals clustered in children but not in adults. (Hoogman et al., 2017). If this is confirmed by future research, this would explain why treatment often needs to be maintained until reaching social maturity, i.e. when the prefrontal cortex is fully mature.

However, starting the treatment early might prevent the alteration of the dog-owner relationship and the use of aversive methods. In addition, this result suggests that the HSHA score could be of a significant help for clinicians to make a prognosis and give information to owners on the length of the therapeutic treatment.

One limit of the present study comes from the fact that only one veterinarian realized all the consultations (i.e. the first author). Thus, the results observed could partly be influenced by the practitioner skills, or by the local network of trainers used to help owners on the behavioral modification part. On the other hand, it provides a consistent way of evaluating the dogs. However, a replication of this work would be needed to validate the results including a higher number of veterinary behaviorists. The relatively small number of cases is an obvious limit to the generalization of our results. However, the results obtained here are highly significant, which provides a real interest to this retrospective study.

In human literature, ADHD has been reported with a larger ratio for males versus females of 2.28:1, but other studies also suggest that female cases are underdiagnosed (Ramtekkar et al., 2010). In dogs, agitated behavior has also been reported more often in Australian male dogs than females, with a 1.7:1 ratio (Col et al., 2016). Nevertheless, in the questionnaire built by Vas and colleagues to measure attention deficit and activity in dogs (2007), no effect of gender was found, which was confirmed by Lit and colleagues (2010). In our study, the gender ratio of 1.4:1, was not significant, suggesting no effect of gender in HSHA in dogs.

With 6 out of 10 males neutered in our HSHA cases, the proportion seems overrepresented compared to the canine French population (TNS SOFRES 2014). This could suggest that owners tried to neuter their dog hoping for an improvement in the behavior. However, the fact that they seek help afterwards, suggests that neutering had no effect on HSHA symptoms.

We could not draw any conclusion concerning breeds. One recently published study has concluded that the differences of impulsivity between dogs within a breed exceed the differences observed between breed (Fadel et al., 2016).

Our clinical HSHA score was correlated to treatment duration and to Fluoxetine dose needed to observe behavior improvement, i.e. minimal efficacious dose. These findings support the idea that HSHA clinical spectrum is ranging from very mild to pervasive and invalidating picture. The use of such score makes consequently more sense than the original two stages. In addition, the most severe cases seem to require life-long medical treatment, which is an important information that could be given to owners quite early in the care process. Considering the complexity of the underlying mechanisms (Carlisi et al., 2016; Dalley & Roiser, 2012) it is illusory to expect that the HSHA clinical score proposed here would be an exhaustive and definitive tool. However, it could be seen as a proposal to collect clinical data on HSHA in a more organized manner across the scientific community and also as a way to have a control on the starting dose for the treatment, especially for dogs with a score under 2 that shouldn't get a higher than 2 mg/kg dose as first intent.

Another interesting perspective of research would be to study the link between this clinical HSHA score and existing questionnaires, such as Vas and colleagues one's (Vas et al., 2007). Making more research concerning quality of life of these dogs and their owners is also a request, and it could be done by following and comparing HSHA clinical score and quality of life questionnaire (Oyama et al., 2017).

Finally, a large communication effort should be continued towards veterinarians and trainers in order to educate them on the importance of looking for HSHA signs such as ingestion of non-edible items, hyposomnia, children of the family being afraid of play sessions with the puppy, bite marks on owner arms. The encouraging long-term results observed in this study (i.e. key role of the medication, improvement of the quality of life, reduction of euthanasia/abandon) gather strong arguments to oppose to the owners that are reluctant to the use of psychotropic medication.

Conclusion

This case report study provides promising results concerning the long-term efficacy and safety of 2 to 4 mg/kg Fluoxetine combined with behavior modification therapy on HSHA dogs. The results obtained via the HSHA clinical score suggest that this disorder includes a wide spectrum of clinical signs, more or less pervasive and invalidating.

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Conflict of interest

The authors declare no conflict of interest

Authorship statement

The idea of the paper was conceived by Sylvia Masson and Emmanuel Gaultier
The experiments were performed by Sylvia Masson
The data were analyzed by Sylvia Masson and Emmanuel Gaultier
The paper was written by Sylvia Masson and Emmanuel Gaultier
All authors have approved the final article

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Studio retrospettivo sulla sindrome di Iper-sensibilità ed Iper-reattività nel cane: risultati di trattamenti con alte dosi di Fluoxetina e proposta di uno score clinico

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Sintesi

Nel modello francese di psichiatria veterinaria, la patologia corrispondente a quella umana, consistente in iperattività ed in un deficit di attenzione, è denominata sindrome di iper-sensibilità – iper-reattività (HSHA) ed include due stadi, differenziabili in base alla gravità dei sintomi clinici. Poiché l'uso del Metilfenidato non è autorizzato in Francia, i cani affetti da HSHA sono trattati normalmente con Fluoxetina (2-4 mg/kg), associata con terapie di modificazione comportamentale.

Lo scopo di questo studio è stato quindi quello di analizzare i risultati a lungo termine di questo tipo di terapia. Nello studio sono stati inclusi 24 cani con diagnosi di HSHA e per ogni cane sono stati analizzati 42 dati descrittivi. Le ragioni principali per la richiesta di una consulenza erano variabili, poiché il cane poteva essere affetto anche da altre patologie comportamentali (33% dei cani). Le lamentele dei proprietari erano legate alla patologia coesistente con l'HSHA (per esempio aggressività verso gli estranei, fobia delle persone) o alla mancanza di autocontrollo del cane (distruzioni, masticazione di oggetti, saltare sopra le persone). La sindrome HSHA altera in modo sostanziale il legame tra cane e proprietario, portando quest'ultimo ad un tale stato di esasperazione da considerare di poter dare il cane in adozione o di volerlo sopprimere (12% dei casi allo stadio 1 della sindrome, 83% allo stadio 2). I risultati della ricerca mostrano che non vi è alcun nesso tra la possibilità di avere accesso al giardino o la quantità di esercizio fisico giornaliero e lo stadio di HSHA in cui il cane si trova. L'83% dei cani ha seguito corsi di educazione cinofila prima di essere portato in consulenza ma senza miglioramenti apprezzabili. Il training sembra essere ancora meno efficace nei casi più gravi, cioè nei cani allo stadio 2. Dopo due mesi di terapia con Fluoxetina ad alte dosi (2-4 mg/Kg), il punteggio medio di miglioramento attribuito dai proprietari fu di 7,2 su10, a differenza del punteggio iniziale di 0 su 10. Non sono stati notati effetti avversi prolungati. Uno score clinico per l'HSHA è stato realizzato per meglio categorizzare i cani e condurre il follow-up, correlandolo con la dose e la durata del trattamento. Per il 54% dei cani è stato possibile effettuare una sospensione della cura in seguito alla remissione dei sintomi. Questi risultati suggeriscono che lo spettro HSHA può presentare segni clinica di media o elevata gravità. Un inizio precoce del trattamento sembra essere importante per il benessere del cane e per salvaguardare la sua relazione col proprietario ma ciò non garantisce che la cura sia più breve o che vi siano più possibilità di terminarla. In conclusione, alti dosi di Fluoxetina, associate con modificazioni comportamentali, sembrano essere efficaci nel trattare questa sindrome complessa e ben tollerate.