Received: 17 October 2022 | Revised: 21 December 2022 | Accepted: 3 January 2023

DOI: 10.1002/vrc2.571

Vet Record CaseReports

CASE REPORT

Companion or pet animals

Behavioural disorder in a dog with congenital agenesis of the vomeronasal organ and the septum pellucidum

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ABSTRACT

A 1.5-year-old, entire male mongrel dog with a bifid nose and primary cleft palate showed aggressiveness towards unknown dogs despite having adequate canine socialisation and the absence of previous traumatic experiences; furthermore, he does not exhibit sexual behaviour towards females in heat. He was previously treated for fear-related aggression towards unknown people and environmental phobia due to poor human socialisation. Pharmacological treatment with fluoxetine and trazodone, together with behaviour modification, was started without success. Therefore, it was decided to repeat medical tests. CT and MRI revealed a rostral middle raphe ossification defect incompatible with the presence of the vomeronasal organ (VNO) and the absence of the septum pellucidum (SP). The dog was presumptively diagnosed with aggressiveness towards unknown dogs due to an organic cause, a congenital anomaly with agenesis of the VNO and SP. This case shows the importance of both structures in the regular intraspecific interactions of dogs.

KEYWORDS
anatomy, behaviour, bifid nose, diagnostic imaging, septum pellucidum, vomeronasal organ

BACKGROUND

A 'behavioural problem' refers to a behaviour exhibited by an animal that is considered unacceptable by the tutor, regardless of its level of abnormality.[1] Behavioural problems are important for several reasons as well as the main risk factors for relinquishment and dog's euthanasia.[2] Moreover, dog bites in humans are a complex public health issue,[3] and some behavioural pathologies, such as separation anxiety, pose problems in the field of animal welfare.[4,5] Behavioural problems can either be the consequence of pathologies or organic problems or could be purely ethological problems. Historically, medical issues in relation to behavioural problems appear to be become more frequent. In 2013, an unpublished review reported a 23% prevalence in dogs.[6]

A relatively rare congenital anomaly is the bifid nose, also known as 'double nose' or 'cleft nose' (Figure 1). It has frequently been associated with hypertelorism, midline lip clefts and other craniofacial deformities.[7] The genetics of this anomaly have not been well defined, and different investigations suggest a dominant inheritance, but the most common presentation is an isolated event within a family.[8,9] We must consider that there is a breed of hunting dog in Spain named 'Pachón Navarro' and another in Bolivia named the 'Andean Tiger Hound', which has the unusual feature of a bifid nose, and is considered normal and desirable for those breeds. In the third week of gestation, it is believed that the inadequate fusion of the maxillary and median nasal processes gives rise to midline facial anomalies.[10] The interruption of this embryonic process creates the malformation of a part or the whole upper lip, central alveolus and primary palate,[11] which can explain its association with midline lip and palate clefts. It is unknown whether a bifid nose is associated with other craniofacial anomalies and clinical indications. However, agenesis of various brain structures could be an underlying anomaly in some situations.

The vomeronasal organ (VNO) is a sensory structure that is highly specialised in the reception of chemical signals, mainly pheromones and kairomones.[12] Carnivora are identified as the mammalian species that have the most developed and varied types of pheromone-secreting glands.[13] Their secretion plays a critical role in the regulation of socio-sexual behaviour by mediating physiological and behavioural responses.[14] Moreover, pheromonotherapy based on the application of dog-appeasing pheromone (DAP) has been used in dogs. It functions as a pheromonal equivalent of the pacifying pheromone secreted by nursing bitches and exhibits effectiveness in a variety of fear-inducing circumstances. DAP can be used to alleviate separation anxiety symptoms, such as house soiling, vocalisations and damage.[15]

FIGURE 1 A dog with bifid nose, also known as 'double nose' or 'cleft nose'

Regarding the VNO, its degree of development is highly variable among different mammalian groups. In canids, its neuroanatomy has been thoroughly characterised in both dogs[16,17] and foxes,[18] finding that a well-developed VNO is located on both sides of the nasal septum's base in direct topographical relationship to the vomer bone. These immunohistochemical studies have confirmed the activeness of its neurosensory epithelium. Its nerve connections to the accessory olfactory bulb have also been demonstrated,[19] as well as the existence in vivo dogs of functional communication through the nasopalatine duct, which allows pheromones and other chemical signals to access the vomeronasal duct.[20]

In contrast, the physiology of pheromone perception is not completely understood in dogs. A substantial part of the existing information on the mammalian VNO function has been obtained in laboratory rodents. Surgical and molecular techniques have shown that the VNO plays a key role in eliciting innate responses linked to socio-sexual behaviour, but also in modulating reproductive physiology.[21] Thus, aspects as diverse as sexual attraction,[22] agonistic behaviour and individual recognition are mediated in rodents by the VNO.[23] In the case of dogs, the complexity and plasticity of their behaviour,[24] as well as the impossibility of applying surgical and molecular techniques analogous to those performed in laboratory rodents, make it difficult to understand the role played by the chemical signals detected by the VNO.[25] However, a correlation between inflammation of the vomeronasal sensory epithelium and intraspecific aggression was observed in the reports by Asproni et al.[26] and Mechin et al.,[27] which described degenerative and inflammatory processes in the VNO of cats and pigs, respectively. This finding suggests that lesions in the VNO may be the source of behavioural changes, such as deficits in social abilities.

Another neurological structure relevant to our clinical case is the septum pellucidum (SP). It consists of two thin laminae situated caudal to the corpus callosum and cephalic to the fornix (trigonum). The SP is a relevant relay station linked mainly with the hippocampus and hypothalamus; therefore, it is part of the limbic system.[28] It may be regarded as a correlative centre relaying visceral information through

LEARNING POINTS/TAKE HOME MESSAGES

- All behavioural problems have an organic cause until proven otherwise.
- The vomeronasal organ is essential for the sexual discrimination of conspecifics. Its absence reduces sexual behaviour.
- The septum pellucidum is part of the limbic system. It presents functions regarding the consciousness-sleep cycle and the emotional response to the environment. It is also involved in attention and activity, self-maintenance, food finding, sexuality, autonomic-vegetative adaptation modes for homeostasis, fight-and-flight and species maintenance.

FIGURE 2 Hacho, the patient

the hypothalamic autonomic system to the hippocampus, amygdala, habenula and brainstem reticular formation.[29] We must highlight its functions regarding the consciousness-sleep cycle and the emotional response to the environment. It is part of the self-maintenance, food finding, sexuality, autonomic-vegetative adaptation modes for homeostasis, fight-and-flight and species maintenance.[30] Due to the essential part played by the hippocampus in memory and because important connections occur between the SP and the hippocampus through the limbic system, SP is also involved in memory[31] as well as in attention and activity due to the participation of the brainstem reticular formation.[29]

The absence (agenesis) of the SP is usually linked to neurological diseases in humans and can be either part of a developmental brain malformation or can be acquired as a sequel of long-standing substantial hydrocephalus.[29] A rare congenital disorder characterised by the absence of the SP, hypoplasia of the optic chiasma and nerves, and various types of hypothalamic–pituitary dysfunction is septo-optic dysplasia (de Morsier syndrome). This is associated with potential defects of the central midline of the brain,[32] similar to bilateral cleft lip and palate[33,34] where it is common to observe

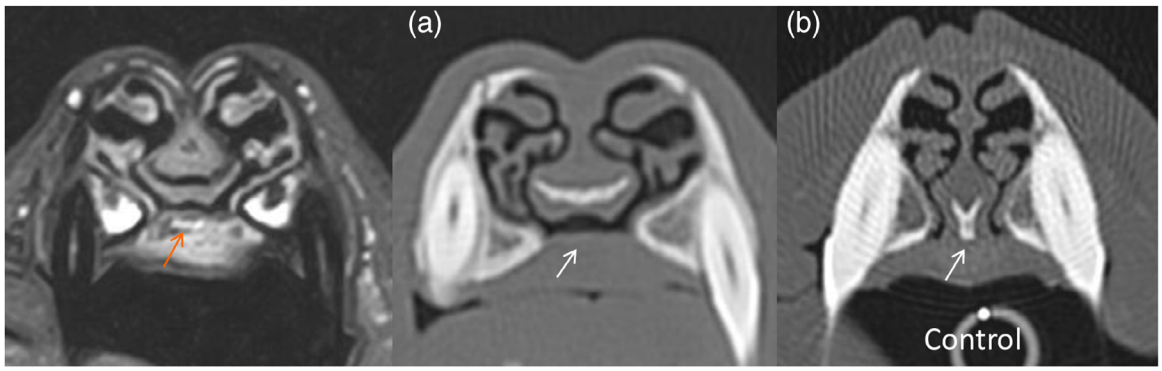

FIGURE 3 Comparative nasal cross-section anatomy at the level of the vomeronasal organ in a T2-weighted MRI (a) and CT images (b), in comparison to a control dog (c). Arrows point to the area of the septal defect affecting the palatine and nasal septum in Hacho (a and b) versus a normal dog (c). A ventral communication between the left and right nasal cavities can also be observed

developmental delay. At the clinical level, abnormalities in the SP can produce learning disabilities and reduced mental development[31] in humans. In addition, abnormalities in the cavum SP, a triangular-shaped space that develops between the two layers of the SP, which normally regresses at 6 months of extrauterine life,[35] are associated in people with antisocial personality disorder and psychopathy,[36] as well as with increased aggression in experimental animals.[37]

CASE PRESENTATION

This case report describes a 1.5-year-old intact male, Hacho, a mongrel dog with a bifid nose and primary cleft palate (Figures 2 and 3). A behavioural consultation was requested at the Behavioural Medicine Referral Service from the Rof Codina Veterinary University Hospital, Faculty of Veterinary Medicine, University of Santiago de Compostela, Lugo, Spain, due to aggressiveness towards unknown dogs, both males and females, despite having adequate canine socialisation and the absence of previous traumatic experiences.

He was born in a country house with a large property and spent the socialisation period with his siblings, parents and other dogs of multiple breeds. The socialisation period occurs between approximately 3 and 13 weeks of age in dogs, although it can vary slightly for different breeds and individuals.[38] He did not leave the property and he was only in contact with the family until the time of adoption. Hacho had a natural weaning until his adoption at 4 months of age. A couple, one of whom worked from home, adopted Hacho and he moved into a flat in a big city. A 3-year-old female mixed-race Podenco dog who was reactive to unknown dogs also lived with them.

From the moment of adoption, Hacho presented different behavioural problems. He tried to escape when unknown people approached him and tended to snap if they attempted to touch him. He attacked cars, motorbikes, scooters and bicycles. He walked back and forth (pacing) in the city, showing fear of traffic, loud sounds and new objects or situations. In addition, he was very active and had difficulties sleeping at night. He also showed multiple and disturbing attention demands, predominantly scratching.

During his first year of life, different clinical veterinary studies were carried out, which included physical, neurological and traumatological examinations, laboratory tests with complete blood count, biochemistry serum and urinalysis, in addition to radiographic imaging. These tests showed a body condition score of 3 out of 9 and mild hip dysplasia. The dog was anaesthetised for a complete oral examination, and head CT was performed to plan both bifid nose and cleft palate reparation surgery. For that reason, at 7 months of age, a gingivectomy was performed with palatoplasty with the extraction of two incisors (101 and 201) to minimise functional problems.

Furthermore, he was diagnosed by another animal behavioural medicine veterinary specialist with fear-related aggression towards unknown people as well as environmental phobia due to poor socialisation with the prior stimuli. Management guidelines were given, and behavioural modifications began resulting in clinical improvement.

When he was 1 year old, he moved to a smaller town, together with the other dog and with the tutor who did not work from home. His anxiety increased, possibly due to spending more time alone and the environmental change. He began to growl, bark and bite into the air after sniffing another dog's urine, which evolved into impulsive aggression towards dogs, regardless of size, age and reproductive status. He had no adverse prior experience with unknown dogs and, until this moment, he had played with all kinds of dogs, always starting the game with a play bow. Furthermore, he did not exhibit sexual behaviour towards females in heat. At this moment, he was referred to our behavioural medicine practice.

TREATMENT

We started with pharmacological and ethological treatment. The pharmacological treatment of choice was the combination of selective serotonin reuptake inhibitor, fluoxetine, 0.5 mg/kg/SID for 1 week, which we increased to 1 mg/kg/SID indefinitely, with the aim of decreasing anxiety, reactivity and impulsivity, and a serotonin antagonist/reuptake inhibitor, trazodone, at 3 mg/kg/BID for its anxiolytic effect.

As for the ethological treatment, different safety guidelines were recommended: avoiding punishment, habituating the dog to a basket muzzle, walking in quiet areas and hours and avoiding other dogs. Dog walks should be taken at times and in places where encountering other dogs is unlikely and with a chest harness attached to a collar, a muzzle and a fixed leash. Moreover, environmental enrichment should be increased

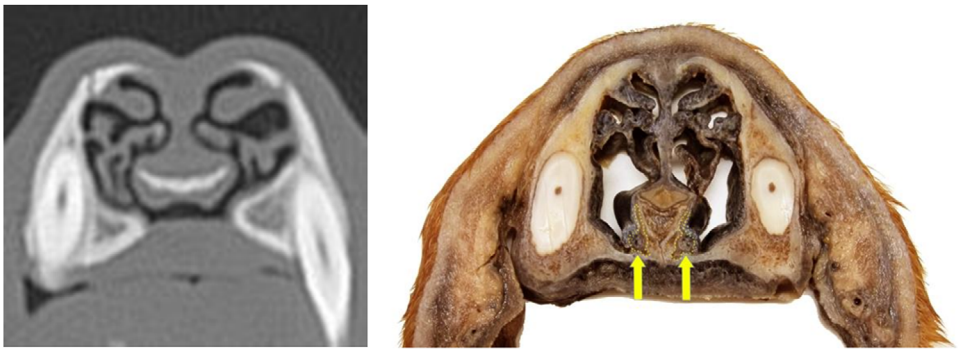

FIGURE 4 The CT image (Hacho, left figure) provided reveals a rostral middle raphe ossification defect affecting the complete rostral osseous nasal septum with the absence of the vomer bone and the palatine–maxillary bone. The cross-section (right figure) is from a dog with no structural problems. The arrows point to the vomeronasal organ. *Source*: Anatomy of the Faculty of Veterinary Medicine of Lugo

with regular physical exercise, encouraging the sense of smell by hiding treats, rotating toys, using interactive and chewing toys and cognitive exercises, and engaging the dog in activities requiring problem-solving (e.g., training and discrimination tasks).

In Hacho's case, the bond between him and his tutor was strengthened by using positive reinforcement and never using positive punishment. Also, relaxation tasks were recommended, and the command 'look' was taught. Finally, behaviour modification through desensitisation–counterconditioning (DCC) drills to unknown dogs by operant conditioning was applied. Systematic desensitisation (SD) is a behaviour therapy technique used to modify behaviours by constructing a gradient of response-producing stimuli (beginning below the threshold that elicits a response) and repeatedly presenting them to the individual at gradually increasing intensities until they no longer elicit a response. SD is often used in conjunction with counterconditioning to facilitate training. This technique involves conditioning an animal to alter its emotional response to a stimulus.[39] When the problematic stimuli are unknown dogs, the dog under treatment is exposed gradually and repeatedly to a figurative dog at closer and closer distances. Approaches to the figurative dog begin by making a 'C' curve. If the dog looks at the tutor voluntarily or after the tutor uses the command 'look', he gets a food reward. Then, the tutor and the dog walk away, and the dog stops receiving rewards. Each session increases the distance or duration. The idea behind this procedure is that the dog, on the one hand, associates approaching another dog with something good (food) but keeps its reactions below the threshold of undesirable responses and, on the other hand, associates the distance with the withdrawal of the reward.

Hacho showed difficulties in learning and cognition, and the improvement was minimal in behaviour modifications. Furthermore, he continued with the same impulsiveness on the street when he saw or smelled an unknown dog's urine. Due to the poor dog's evolution, we decided to re-investigate organic problems.

INVESTIGATIONS

Hacho seemed to have had a correct canine socialisation period. Raised with his siblings and other dogs from different breeds, had natural weaning and had no bad experiences with other dogs. Firstly, we decided to rule out organic problems such as neurological, traumatological, endocrine and metabolic problems that could explain his condition.

Physical, neurological and traumatological examinations, complete blood analysis and hip radiography were repeated, without alterations concerning the previous ones. Therefore, it was decided to make complementary tests. The CT was first performed, for economic reasons, and after observing some abnormalities, MRI was performed to proceed with the complete study of the animal.

The CT and the MRI revealed a rostral middle raphe ossification defect that affected the complete rostroventral osseous nasal septum, extending to the rostral aspect of the vomer bone and the palatine–maxillary bone, compatible with the absence of the VNO (Figures 3 and 4). Intracranially, a complete absence of the SP was also observed between both lateral ventricles of the brain (Figure 5).

Therefore, the presumptive diagnosis is aggressiveness towards unknown dogs by organic cause due to congenital anomaly: agenesis of the OVN and SP.

OUTCOME AND FOLLOW-UP

After 15 days of therapy, Hacho got worse despite the tutor complying with the guidelines, even having at least one daily walk through the woods. The dog started showing more anxiety during walks and started snapping again at people who passed by when he was on a leash. The worsening coincided with the rise of fluoxetine to 1 mg/kg/SID, so we changed to paroxetine 0.5 mg/kg/SID for 1 week and then went up to 1 mg/kg/SID indefinitely. Paroxetine is useful in aggressive dogs and those suffering from generalised anxiety. Unlike fluoxetine, paroxetine has weak effects on the neuronal reuptake of norepinephrine, producing more sedation, which was beneficial in this case. Although paroxetine seems more appropriate in this case, we used fluoxetine as the first-choice serotonergic drug in the treatment of intraspecific aggression because several studies have examined its efficacy.[40–42] On the other hand, the evidence of the efficacy of paroxetine in canine behaviour disorders is limited to generalised anxiety.[43]

Within 15 days of the onset of paroxetine, anxiety and aggressiveness towards unknown people decreased.

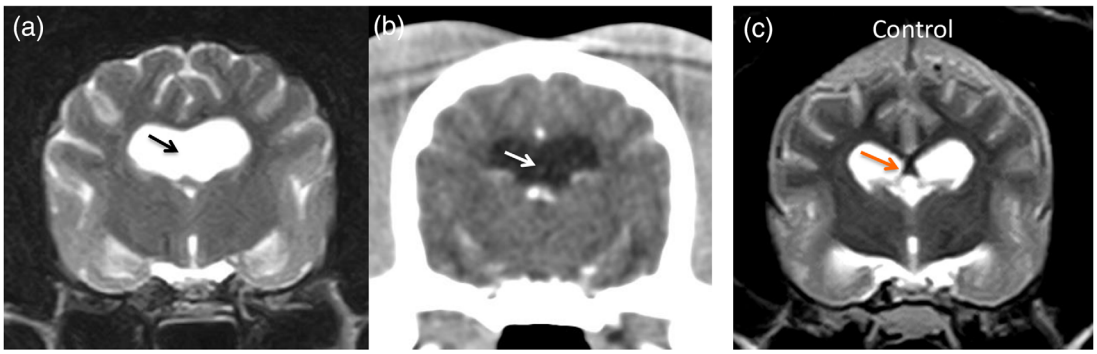

FIGURE 5 Comparative brain cross-section at the level of the interthalamic adhesion in Hacho (a and b) and in a control dog (c) using T2-weighted MRI images (a and c) and CT. (a) T2-weighted image indicating the absence of the septum pellucidum (SP) (orange arrow). (b) CT image showing absence of the SP (orange arrow). (c) T2-weighted image at the same level in a control dog with a well-developed SP (orange arrow)

However, the demands of attention and excessive activity continued during the night. After raising the trazodone dose to 5 mg/kg/BID, Hacho began to sleep at night without disturbing his tutor, and his body condition progressively reached body condition score (BCS) 5 out of 9 after 1 year from the start of treatment.

After 1 month with the new pharmacological treatment, behavioural modification techniques were resumed. Firstly, we reinforced the positive habituation to the muzzle, the 'come away' command, the relaxation protocol and the 'look' command. Hacho was asked to look every time he saw a dog on the street until it disappeared from Hacho's sight. In case he barked, they fled the situation without saying anything.

Furthermore, in our centre, we resumed desensitisation and operant conditioning with other dogs. A class was held every 15 days for a year, and we got him to ignore the dog with a short distance and to be aware of the tutor. This was applied on the street, getting to walk ignoring the unknown dogs, but if any of the dogs maintained visual or physical contact with him, Hacho would snap regardless of size, sex and reproductive status.

During the first year of treatment, several whole male dogs tried to attack him. We decided to put an implant of deslorelin 6 months after the start of treatment to avoid new bad experiences with other male dogs and to see the effect of castration on the aggressive behaviour of the dog. The implant decreased the only sexually dimorphic behaviour he performed (marking behaviour) and increased Hacho's fear of people and noises. Therefore, gonadectomy was ruled out in this case.

After a year and a half of treatment, he has been able to walk through rural areas without a leash ignoring dogs as long as they do not have any contact with him.

DISCUSSION

The bifid nose is a relatively uncommon malformation that falls within a spectrum of midline facial and brain abnormalities. It is frequently associated with midline lip cleft lip and a variety of other congenital abnormalities in humans.[7] The absence of the SP is also associated with potential defects of the central midline of the brain[32] and with bilateral cleft lip and palate.[33,34] VNO is located on both sides of the base of the nasal septum in direct relation to the vomer bone.[17] In this case, the abnormalities in the midline facial and brain are at the base of the bifid nose, cleft palate and the absence of SP. Moreover, the absence of the vomer bone and the palatine–maxillary are at the base of the presumptive agenesis of the VNO.

To our knowledge, there are no precedents in the literature describing the agenesis of the VNO in dogs or in any other mammalian species. Only the study of the surgical repair of a bifid nose combined with a cleft of the primary palate in a 1-year-old dog[44] describes an individual with a malformation similar to the one observed in our dog. They performed the same gingivectomy with palatoplasty surgery carried out in Hacho, and the CT images shown in this work are compatible with the absence of the VNO. Unfortunately, neither a specific imaging study to verify the possible absence of the VNO nor a behavioural study of the dog was performed in this report.

The case presented here establishes a possible correlation between the absence of a vomeronasal system and the behavioural changes that a male dog may present. The studies conducted in experimental rodents show a wide range of behavioural, social, reproductive and other deficits,[45–49] which coincides with what we have observed in Hacho. Male mice that had undergone surgical removal of the VNO were observed to lose interest in the urine of females in heat.[48] Likewise, Cross et al.[50] found that ablation of the VNO in peripubertal mice decreased sexual odour preferences and neural activity in response to opposite-sex odours. Beyond laboratory rodents, the effects of surgical ablation of the VNO have been assessed in farm animals. Booth and Webb[51] found that in rabbits undergoing cauterization, impaired access of molecules to the vomeronasal duct produced a lack of interest in mating in females. They did not become pregnant and did not demonstrate the primary increase in tonic plasma levels of luteinising hormone that is necessary for ovulation to occur. The same authors found that ewes that had their VNO rendered non-functional by cauterisation of the nasopalatine duct showed deficits in maternal behaviour.[52] So, the agenesia of VNO could be related to the absence of sexual behaviour towards females in heat, as in the reported case. Regarding females, vomeronasal agenesia might be the organic basis for certain changes in maternal behaviour in domestic female dogs.

On the other hand, considering that there are different articles that correlate the absence of the VNO with a decrease

in intermale aggression in rodents[46,53] it is surprising that Hacho presents an intact expression of intermale aggressive behaviour. However, the most recent study by Trouillet et al. in mice, unlike previous studies, selectively suppressed the vomeronasal receptors family V1R, the only ones present in the VNO of dogs,[54] observing that aggressive behaviour between males remained intact despite the lack of expression of these V1R receptors. Because of this, aggression would be reduced only if the vomeronasal receptor family V2R was suppressed in Hacho, as it is in mice, but it is known that dogs lack functional V2R receptors.[55] If we consider the latest results and that Hacho shows aggressiveness towards males and females, his behaviour could be compatible with the agenesis of VNO. More studies are necessary to clarify the importance of VNO in canine behaviour.

No previous reports about the relationship between the agenesis of the SP and canine behaviour have been published, and until now, the lack of SP on CT or MRI has been considered an accidental finding. However, the lesions of the septum result in increased aggression and disinhibited behaviour in a wide range of animals (rats, hamsters, mice, cats and monkeys),[36,37] which is a shared behaviour in our patient. In humans, it was observed that the SP is part of the limbic system and participates in consciousness and sleep, as well as in the emotional response to the environment.[30,56] In this case, it could explain why Hacho did not sleep at night and, possibly, the altered emotional response to environmental stimuli. In addition, SP is involved in sexuality, so his absence could diminish it. Finally, SP is part of the limbic system, which plays an important role in the emotional system, being able to influence its responses mediated by fear.[57] We emphasise that a limitation of the present study is the inability to discriminate the individual contribution of the VNO and the SP to Hacho's behavioural changes. Given the involvement of both structures in both sexual and social behaviours, it is likely that both ageneses act synergistically.

However, scientific evidence for the behavioural characteristics of agenesis of the SP in animals is still very limited, and so, to the best of our knowledge, this current clinical case is the first investigative research on behavioural changes, especially aggression, possibly caused by the absence of SP in dogs. Nevertheless, more studies are necessary in order to clarify the importance of SP in canine behaviour.

In conclusion, a veterinary multidisciplinary approach is necessary to solve some kinds of animal pathologies. Veterinarians specialising in animal behaviour should always suspect an organic problem until all tests have been carried out correctly, considering the possible evolution of diseases over time. Uniquely when the organic problems have been discarded, we can think of an exclusive behavioural problem.

This is the first reported case of a living dog with the absence of the VNO and SP, suggesting the importance of both structures in the dog's intraspecific communication and social interaction. The dog is probably unable to communicate adequately, showing inhibition of his sexual behaviour and impulsive aggressiveness.

AUTHOR CONTRIBUTIONS

Veterinarians in charge of the clinical case: Susana Muñiz de Miguel and Ángela González Martínez. *Veterinarian in charge of executing and analysing the CT and MRI*: José Daniel Barreiro Vázquez. *Veterinarians in charge of investigating the case*: Susana Muñiz de Miguel, Ángela González Martínez, Pablo Sánchez Quinteiro and Irene Ortiz Leal. *Paper writers*: Susana Muñiz de Miguel, Ángela González Martínez, José Daniel Barreiro Vázquez and Pablo Sánchez Quinteiro.

ACKNOWLEDGEMENTS

The authors would like to thank Hacho, a very special dog, and to all the people who have been part of this project.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

ETHICS STATEMENT

The authors confirm that they have adhered to the ethical policies of the journal, as noted on the journal's author guidelines page. No ethical approval was required, as this is a case report, and all treatment was consented to by the tutor.

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How to cite this article: Muñiz-de Miguel S, Barreiro-Vázquez JD, Sánchez-Quinteiro P, Ortiz-Leal I, González-Martínez ÁG. Behavioural disorder in a dog with congenital agenesis of the vomeronasal organ and the septum pellucidum. Vet Rec Case Rep. 2023;11:e571. https://doi.org/10.1002/vrc2.571

IMAGE QUIZ

Figure 4. The CT image (Hacho, left figure) provided reveals a rostral middle raphe ossification defect affecting the complete rostral osseous nasal septum with the absence of the vomer bone and the palatine–maxillary bone. The cross-section (right figure) is from a dog with no structural problems. The arrows point to the vomeronasal organ. *Source*: Anatomy of the Faculty of Veterinary Medicine of Lugo.

MULTIPLE CHOICE QUESTION

What is supposed to be anatomically at the CT image given in a normal dog?

a) VNO
b) Nasal septum separating both nasal cavities
c) Palatine fissure divided in two separate foramina
d) Palatine process of incisive bone

POSSIBLE ANSWERS TO MULTIPLE CHOICE QUESTION

All answers are correct.

CORRECT ANSWER

VNO

The VNO is a paired, tubular formation located on both sides at the base of the nasal septum and in direct relation to the vomer bone, to which the lateral surface is closely coupled. This is the reason why, in this case, it is incompatible with the presence of the VNO.