MARTA SOFIA DE ALMEIDA LOURENÇO

IDIOPATHIC VESTIBULAR SYNDROME: METHODOLOGICAL APPROACH AND DESCRIPTIVE STUDY OF NINE CLINICAL CASES

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Faculdade de Medicina Veterinária

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Dedications

First, I thank to Dr. David Ferreira for guiding me while developing my dissertation and to Dr. João Ribeiro for letting me work at *Clínica de Referência Veterinária*.

I also dedicate this work to my parents and grandmother, for always believing in me and in my capacity, by the wise councils. And I thank you, dad, for being also an excellent teacher for me and my colleagues.

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To *Kiko* and *Fred*, for being my "*paw*rtners" in crime.

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Abstract

The idiopathic vestibular syndrome (IVS) is characterized by a lesion of the vestibular portion of the vestibulocochlear nerve (VIII). There is no known etiology and it usually leads to vestibular clinical signs with an acute onset and severe presentation, which enter in remission in three to four weeks, without any instituted medication.

This study intends to analyse and compare the results of the neurological examinations and the respective ancillary diagnostic exams with the disease progression and prognosis of each animal suspected with idiopathic vestibular disorder, followed at *Clínica de Referência Veterinária* (RRV). In general, the evolution of the described clinical cases was according with the literature.

The proposed causes for IVS are early Otitis interna/media, abnormal production, circulation and absorption of the endolymphatic fluid, neuritis of the vestibular portion of the vestibulocochlear nerve, *Cuterebra* larvae aberrant migration (not present in Portugal) and herpesvirus-1 infection of vestibular labyrinth and ganglion in dogs.

Abbreviations

ACTH – Adrenocorticotropic Hormone

ALP – Alkaline Phosphatase

ALT – Alanine Aminotransferase

AST – Antibiotic Sensibility Test

BAER – Brainstem Auditory Evoked Responses test

BPPV – Benign Paroxysmal Positional Vertigo

BUN – Blood Urea Nitrogen

CSF – Cerebrospinal Fluid

CN – Cranial Nerve

CNS – Central Nervous system

CVD – Central Vestibular Disease

CT – Computed Tomography

DAMNIT-V – Degenerative; Anomalous; Metabolic; Neoplastic, Nutritional; Inflammatory, Infectious, Immune mediated, Iatrogenic (toxic), Idiopathic; Traumatic; Vascular.

EEG - Electroencephalogram

FIP – Feline Infectious Peritonitis

FMV-UL – Faculdade de Medicina Veterinária da Universidade de Lisboa

FLAIR – Fluid attenuation Inversion Recovery

fT4 – Free Thyroxine

GABA - Gamma-Amino Butyric Acid

GME – Granulomatous Meningoencephalitis

IV – Intravenous

IVS – Idiopathic Vestibular Syndrome

MLF – Medial Longitudinal Fasciculus

MRI – Magnetic Resonance Imaging

NSAID's – Nonsteroidal Antinflammatory Drugs

OIM – Otitis interna/media

PVD – Peripheral Vestibular Disease

RDW – Red Cell Distribution Width

RRV – Clínica de Referência Veterinária

SBP – Systolic Blood Pressure

SC – Subcutaneous

STIR – Short Tau Inversion Recovery

TIA – Transient Ischemic Accidents

TP – Total Protein

TSH – Thyroid Stimulating Hormone

TT4 – Total Thyroxine

T1W – T1 weighted image

T2W – T2 weighted image

T4 – serum Thyroxine

UMN – Upper Moto Neuron

UTI – Urinary Tract Infection

VHS – Vertebral Heart Score

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1. Casuistry

The work presented in this thesis results from an internship in small animal neurology, and neurosurgery, in the *Clínica de Referência Veterinária* (RRV), a neurological referral Centre, housed in Alcabideche, Cascais (Portugal), under the clinical supervision of Dr. João Ribeiro. This internship was performed between September 19th (2016) and March 31st (2017), in a total of seven months with between 43 to 45 clinical working hours per week.

During this internship, I had the opportunity to experience various clinical routine activities as animal and owners' reception, help in the neurological medical exams, preparing the animals for surgeries and MRI exams, including anaesthesia preparation and monitoring. This internship was essential to the improvement of my neurological knowledge, whilst allowing me to begin almost all the animal clinical exams, having the opportunity to participate in most of the neurological examinations to better find the lesions' neurolocation. Additionally, it significantly improved my communication skills with pet owners in a personal and medical point of view

During this internship, I followed several clinical neurologic cases, including herniated discs, meningoencephalitis (mostly granulomatous meningoencephalitis), epilepsy (generally idiopathic or due to encephalitis), cranial and vertebrae trauma, degenerative myeloencephalitis, arachnoid cysts and diverticula and many other diseases. I have also participated in anaesthetics monitoring and surgical procedures, including hemilaminectomy for hernia and arachnoid cyst resolution, vertebrae fixation (after trauma), extirpation of medullary tumours, foreign bodies removal (one case, for medullary projectile removal).

During the internship, it was performed a retrospective search in the database of the *Clínica de Referência Veterinária* of all animals suspected of having vestibular disease, during the period between 2011 and 2017. The inclusion criteria were animals with neurologic examination compatible with possible vestibular disease, animals that were submitted to complete neurological examination, to MRI/CT (with or without CSF collection and analysis), to a basic or complete blood cell count and biochemical serum analysis (including thyroid function evaluation).

2. Introduction

2.1. Vestibular syndrome – brief description

Vestibular system is responsible for maintaining the body balance, along with visual and general proprioception systems. This system is the special proprioception receptor (including specific receptors that respond to head movements and positions), and allows the adequate ocular, cervical, thoracic and limb placement relatively to the head position and motion, in order to keep balance (Kent *et al*, 2010; Rossmeisl, 2010; Lahunta & Glass, 2009; Chrisman, 1980; Schunk & Averill, 1983).

When some of the vestibular apparatus structures (described below) are compromised it leads to vestibular and balance dysfunction, characterized by a group of typical clinical signs including head and body posture and gait abnormalities, as well as alteration of physiological ocular movement and position (Rossmeisl, 2010; Lowrie, 2012).

2.2. Known origins leading to vestibular syndrome

The vestibular system includes peripheral (outside the brain stem) and central (within the brain stem and cerebellum) vestibular components. Vestibular syndrome can be classified as central or peripheral, according to the compromised anatomical structures (Lowrie, 2012; Dewey & Costa, 2016; Rossmeisl, 2010).

The peripheral components of the vestibular system are located within the petrosal portion of temporal bone, along with the auditory system receptors. The peripheral system includes receptor structures located in the membranous labyrinth in the inner ear, and peripheral axons of the vestibular ganglia and nerve, components of the vestibulocochlear nerve (cranial nerve VIII) (Lowrie, 2012; Dewey & Costa, 2016).

The central components of the vestibular system include the vestibular nuclei (medulla oblongata), and vestibular projections to rostral brain stem, to cerebellum (cerebellar nuclei) and long tracts to spinal cord (Rossmeisl, 2010; Lowrie, 2012). Specific cerebellar lesions can lead to paradoxical central vestibular disease (Lahunta & Glass, 2009).

It is essential to get a fully neurological examination to access a proper neuroanatomic location and differentiate the vestibular syndrome whether as peripheral or central. Lesions affecting peripheral and central vestibular system have different diagnosis, treatment and prognosis. Usually, central vestibular diseases have a worse prognosis) (Lowrie, 2012).

2.3. Anatomical and neurofunctional basis

2.3.1. Inner ear anatomy

In the inner ear, located in the petrosal component of the temporal bone, it is possible to differentiate two neurologic afferent systems that were formed together during the embryologic development: the auditory system (Special Somatic Afferent System) and the vestibular system (Special Proprioception System) (Lahunta & Glass, 2009). Both receptors have ectodermal origin but are contained within a mesodermal derived structure (the temporal bone) (Lahunta & Glass, 2009; Dewey & Costa, 2016).

The receptors of the vestibular system are housed inside the bony labyrinth, a fluid-filled ossified structure, located within the petrous portion of the temporal bone (Figure 1) (Lahunta & Glass,2009; Dewey & Costa, 2016).

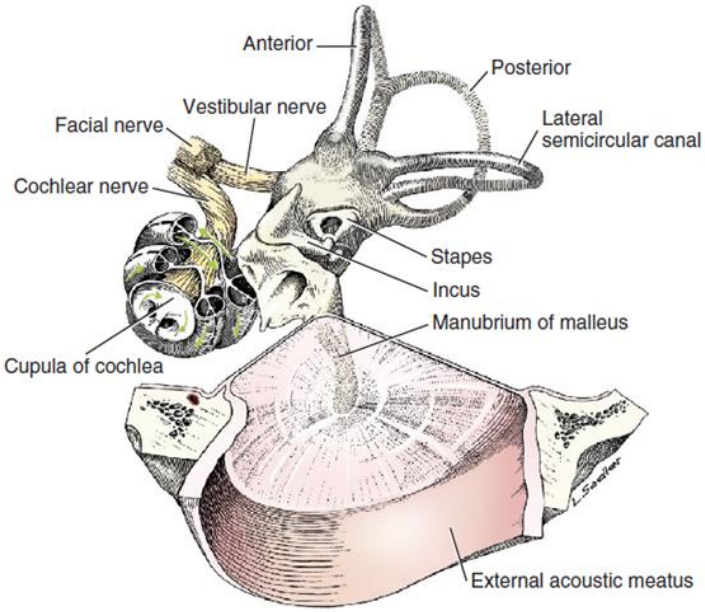

Figure 1 - Anatomy of the tympanic membrane, middle ear ossicles and inner ear (Evans & Lahunta, 2013).

The bony labyrinth consists of three continuous portions (fluid-filled structures) which include the large vestibule, the three semi-circular canals and the cochlea (arising from the vestibule). Each end of the semi-circular canals has a dilation, the *Ampulla* (figure 2) (Lahunta & Glass, 2009).

The fluid contained inside the three bony portions is called *perilymph*, similar to cerebrospinal fluid, from which is probably originated (Lahunta & Glass, 2009).

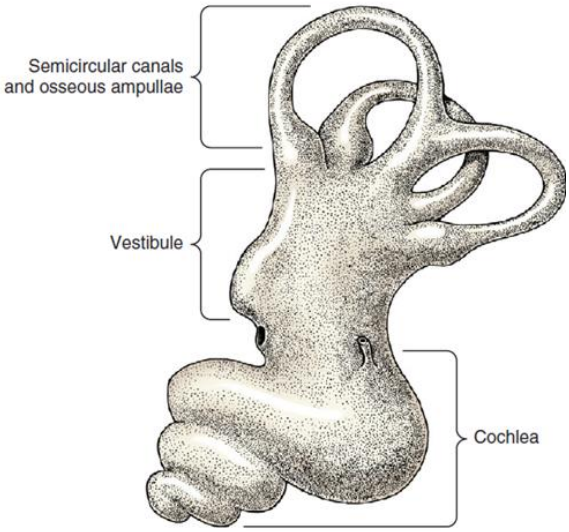

Figure 2 - Anatomy of the bony labyrinth (Evans & Lahunta, 2013).

The bony labyrinth lodges the membranous labyrinth, which is divided into four communicating compartments (filled with fluid called *Endolymph*, probably derived from the blood vessels supplying one of the cochlear duct walls). These structures are the three semi-circular ducts (inside the bony semi-circular canals), the *Saccule* and the *Utriculus* (housed inside the bony vestibule) and the cochlear duct (within the bony cochlea) (Figure 3) (Lahunta & Glass, 2009).

Each semi-circular duct is perpendicular to the other: two vertical ducts, the anterior and the posterior and one in horizontal orientation, which is the lateral one. One end of each semi-circular duct has a dilation, the *Ampulla*, that connects to *Utriculu*s (Lahunta & Glass, 2009).

The utriculus is connected to both semi-circular duct ends and is adjacent to the saccule (Figure 3) (Lahunta & Glass, 2009).

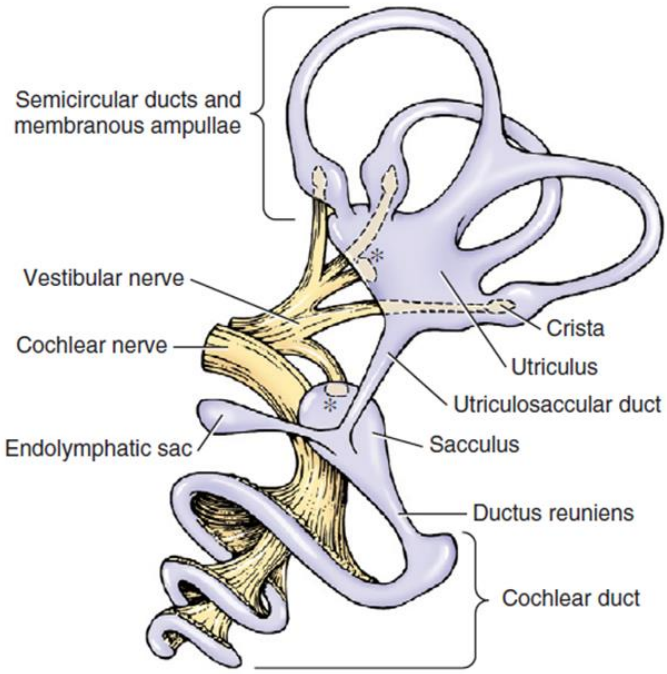

Figure 3 - Schematic of the membranous labyrinth (Evans & Lahunta, 2013).

Each semi-circular duct has a synergistic pair on the opposite side (in a parallel plane). The synergistic pairs are the left and right lateral ducts, the left anterior and right posterior ducts and the left and right anterior ducts (Lahunta & Glass, 2009). When the vestibular neurons of one duct are stimulated, the corresponding neurons of the synergistic pair in the opposite side are inhibited (Lahunta & Glass, 2009).

The *Ampulla* has a transverse ridge composed by a proliferation of connective tissue, the *Crista*. Its internal surface consists on columnar neuroepithelial cells, covered in all its extension by a protein-polysaccharide material with gelatinous texture, the *Cupula* (Lahunta & Glass, 2009).

The *Crista*'s neuroepithelium comprises the hair and supporting cells. In the base of the hair cells synaptic contact is established with the neuronal dendritic zones of the vestibular portion of cranial nerve VIII. The luminal surface of hair cells consists of forty to eighty modified microvilli (*Stereocilia*) and one modified cilium (*Kinocilium*) that projects into the *Cupula* (Lahunta & Glass, 2009).

The endolymph movement deflects the *Cupula* (transversely oriented with the endolymph flow), promoting the movement of the *Stereocilia* and stimulating the neuronal dendritic zone of vestibular neuron (Lahunta & Glass, 2009).

When the *Cupula* deflects it is possible to induce neuronal activity due to anatomical orientation of the stereocilia relative to the *Kinocilium* (Lahunta & Glass, 2009).

As the three semi-circular ducts are oriented at right angle to each other, head movement (in any plane and angle) leads to *Cupula* and *Crista* activation, stimulating vestibular neuron activity (Lahunta & Glass, 2009).

The receptor of both *Utriculus* and *Saccule* is called *Macula,* an oval shaped plaque, where the membranous labyrinth proliferates. Its surface is composed by columnar neuroepithelium, including hair and supporting cells. The neuroepithelium is also covered with a gelatinous structure called *Statoconiorum membrane,* over which lies the *Statoconia* (otoliths, that consists of calcareous crystalline bodies) (Lahunta & Glass, 2009).

Similarly to the *crista*, the macular hair cells also have luminal projections, the *Stereocilia* and *Kiniocilia,* adjacent to the *Statoconiorum membrane*. The *Statoconia* flow against the hair cells causes movement of the *Stereocilia*, stimulating the neuronal dendritic zone and establishing synapse with the base of the hair cells (Lahunta & Glass, 2009).

The saccular macula is vertically oriented (in a sagittal plane) while the utricular macula is horizontally oriented (in a dorsal plane). Gravity influences the *Statoconia* position relative to the hair cells leading to the perception of head static position and linear acceleration or deceleration, controlling the static equilibrium (Lahunta & Glass, 2009).

Utricular macula is the main receptor for head posture changes, and saccular macula is more specific for vibrational and loud sounds (Lahunta & Glass, 2009).

2.3.2. Vestibular pathways

The vestibular axons, form the vestibular component of the vestibulocochlear nerve, proceed to the lateral surface of the rostral medulla oblongata at the cerebello-medullary angle after leaving the internal acoustic meatus (Lahunta & Glass, 2009).

Then the vestibular axons course entering the medulla between the caudal cerebellar peduncle and the spinal tract of the trigeminal nerve. Most of these axons end in the vestibular nuclei and pons, but some continue directly into the cerebellum via the caudal cerebellar peduncle, ending at the fastigial nucleus, originating the direct vestibulocerebellar tract (Lahunta & Glass, 2009).

Additionally, proprioceptive pathways from the limbs and body (the spinocerebellar tracts) proceed to the cerebellum via the caudal cerebellar peduncle. The efferent pathways, the vestibulospinal tracts, will be responsible to deliver the information to the muscles controlling appendicular and axial components systems (Dewey & Costa, 2016).

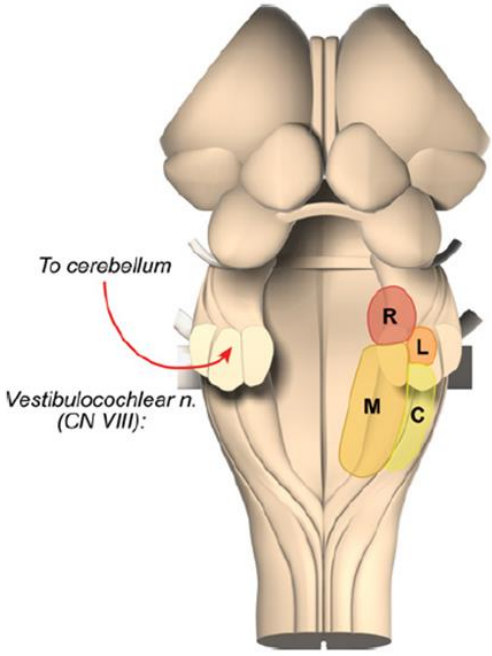

Figure 4 - Schematic of vestibular nuclei (dorsal aspect of the brainstem; the cerebellum was removed). M: medial vestibular nucleus; C: central vestibular nucleus; L:lateral vestibular nucleus; R: rostral vestibular nucleus (Dewey & Costa, 2016).

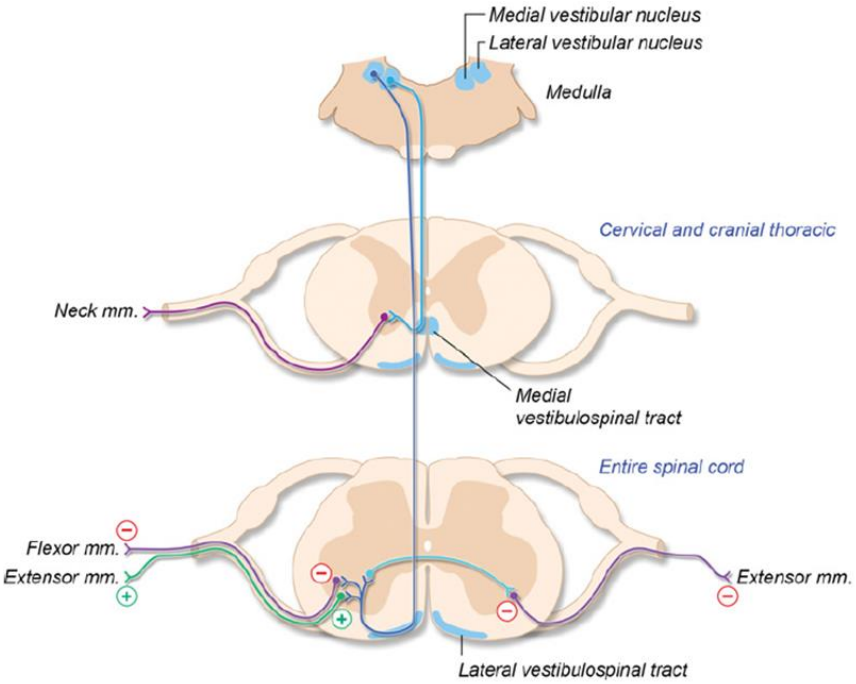

Figure 5 - Schematic of the course of the lateral vestibulospinal tract (Dewey & Costa. 2016).

2.3.3. Cerebellar importance in the vestibular syndrome

Cerebellum is the organ responsible for the adequate processing of motor function, helping coordinating the posture, muscle tone and unconscious proprioception (body position in space) and ensuring the coordination for segmental movements to achieve a correct posture (Dewey & Costa, 2016).

The cerebellum can also be functionally divided in three distinct components: the *Cerebrocerebellum* (lateral hemispheres and dentate nucleus; control the limb movement and cognitive process of movement initiation), *Spinocerebellum* (vermis and intermediate zone, medial to the hemispheres; it controls unconscious motor movements and muscle tone to maintain gait and posture, receiving somatosensory information from the spinal cord and being associated to the *Fastigial* and *Interposital* nuclei), and *Vestibulocerebellum* (Dewey & Costa, 2016; Hahn & Thomson, 2012).

The *Vestibulocerebellum* coordinates equilibrium, vestibular reflexes as well as head and eye movement and consists on the *Flocculonodular Lobe* and *Fastigial Nucleus* (Dewey & Costa, 2016).

Vestibulocerebellum primarily receives afferent input from the vestibular labyrinth, which comes directly from vestibulocochlear connections and indirectly from the medullar vestibular nuclei. It also receives visual information from the pontine nuclei

where the corticopontine tracts deliver information from the rostral colliculi and lateral geniculate nuclei through the middle cerebellar (Lahunta & Glass, 2009; Cunningham & Klein, 2007; Dewey & Costa, 2016).

The medullar vestibular nuclei receive efferent projections from some of the Purkinje neurons (from the vestibulocerebellum) which primarily arise from the flocculonodular lobe. The vestibular nuclei also receive projections from fastigial nucleus and projects the lateral and medial vestibulospinal tracts, running in the ventral funiculi of white matter (Lahunta & Glass, 2009; Dewey & Costa, 2016).

In some cases, unilateral lesions affecting the *Flocculonodular Lobe* of the cerebellum and the supramedullary portion of the caudal cerebellar peduncle can produce a paradoxical central vestibular disorder with an erroneous pattern. Contrary to the most central and peripheral vestibular disorders producing ipsilateral *head tilt*, ataxia and *circling*, the paradoxical central vestibular impairment lead to a contralateral *Head tilt*, ataxia, *circling* and a nystagmus with the fast component toward the side of the lesion. However, it may produce ipsilateral cranial nerve deficits and postural reaction deficits which may help determining the neurolocation of the lesion (LeCouteur, 2003).

Usually this disorder is induced by space-occupying lesions (i.e. neoplasms or granulomatous meningoencephalitis) involving the Cerebellar general proprioceptive system (as previously described), which may produce ipsilateral postural reaction deficits and proprioceptive ataxia (including dysmetria) (Schunk,1988).

Since the *Vestibulocerebellum* output is direct (not depending on the deep cerebellar nuclei path), it has inhibitory influence on the vestibular nuclei. Thus, once there is a unilateral lesion involving the *Vestibulocerebellum*, the inhibition of the vestibular nuclei is decreased or even absent, leading to a higher activity on the affected side than the normal opposite side. This uneven input is perceived as the animal turning to the lesion side, which leads to "compensatory" vestibular signs (contralateral head tilt, ataxia, circling and nystagmus with the fast phase toward to the side of the lesion) (Hahn & Thomson, 2012).

Additionally, proprioceptive pathways from the limbs and body (the spinocerebellar tracts) proceed to the cerebellum via the caudal cerebellar peduncle, may also lead to ipsilateral proprioceptive deficits (Hahn & Thomson, 2012). Ipsilateral paresis is also

possible due to the impendence to the UMN nuclei of the brainstem (Hahn & Thomson, 2012).

Gait and posture alterations may include symmetric truncal ataxia, dysmetria (commonly hypermetria) and wide-based stance. Some animal suffering from cerebellar impairment with acute onset may develop decerebellate posture: tonic extension of the thoracic limbs and flexion of pelvis and pelvic limbs, known as *opisthotonos*; pelvic limbs can also be extended if the ventral part of the cerebellar rostral lobe is involved. These clinical signs can disappear in a few days giving place to another chronic cerebellar signs as ataxia or intention tremor (Lorenz *et al*, 2011).

Intention tremor can occur while the animal is moving (intention) or resting (postural), and usually involves the head. Intention tremor is more pronounced when the animal attempts to move for a specific purpose, like eating or drinking. Postural tremors consist of side-to-side and forward-backward head movements. Both postural and intention tremor are absent while the animal is relaxed or asleep and is not considered an involuntary movement (Lorenz *et al*, 2011).

Sometimes some eye oscillations and dysmetria can occur during movement and gaze fixation. Quick changes in head position can induce nystagmus (quick and slow). Diffuse cerebellar lesions can produce menace response impairment in some animals, despite both vision and facial nerve function may be unaltered. Anisocoria and ptosis are also reported in some cases (Lorenz *et al*, 2011).

Summarizing, the vestibular structures described above which may eventually be affected in vestibular disorders are in Table 1.

Table 1 - Vestibular structures that may be involved in a respective vestibular disorder (Negreiros, 2012)

VESTIBULAR DISORDER	VESTIBULAR PATHS THAT MAY BE AFFECTED
CENTRAL (Including the vestibular nuclei and the Vestibular projections to the Spinal Cord, Cerebellum and Brain Stem)	Vestibular nuclei (lateral walls of fourth ventricle): rostral, medial, lateral and caudal nuclei
	Spinal cord projections (via the vestibulospinal tracts and descendent medial longitudinal fasciculus)
	Cerebellar projections (via the caudal cerebellar peduncle) and terminating areas: flocculonodular lobe and fastigial nucleus
	Brain Stem projections (medial longitudinal fasciculus)
PERIPHERAL	Receptor organs of the vestibular division of CN VIII
	Peripheral axons oh the vestibular division of CN VIII
PARADOXICAL (central)	flocculonodular lobe (Cerebellum)
	Supramedullary portion of the caudal cerebellar peduncle

2.4. Main clinical signs of vestibular dysfunction

Vestibular system provides identical tonic input to each side of the head. Thus, activation of vestibular nuclei stimulates the ipsilateral extensor and contralateral flexor limbs and trunk musculature, which allows a correct and balanced body position in space. However, when the vestibular apparatus of one side is impaired it will not enable the ipsilateral normal activation of the vestibular nuclei, leading to an unbalanced bilateral tonic input. This imbalance may produce a moderate stimulation of the extensor musculature of the normal side (contralateral to the lesion) and a lack of it ipsilateral to the lesion. Thus, once the contralateral extensor musculature receives the most vestibular input, it may lead to a deviation of the body to the impaired side, producing typical clinical signs like *head tilt*, *circling*, *leaning* or *falling* to the abnormal side (Dewey & Costa, 2016).

Vestibular impairment usually leads to unilateral and asymmetric clinical signs. The most common signs are head tilt, loss of balance, asymmetric rolling, ataxia (with propensity to lean or fall, usually to one side; the strength is always preserved), spontaneous or positional nystagmus and/or strabismus (Negrin et al, 2010; Schunk, 1988). In some cases, the patient can show circling (usually to the affected side), trunk curvature (which concavity is ipsilateral to the lesion), and can lean or fall to the affected side or leaning against the walls for additional support. These signs can differ in type or display according

the lesions' origin (some are only displayed in central or peripheral disease and it expression may vary) (Schunk, 1988). Central versus peripheral signs will be further described and differentiated. Some animals can roll to the side of the head tilt while suffering from a vestibular dysfunction at an acute stage. Such sign is exhibited due to a decrease in the limb extensor tone on the affected side and an increase in the contralateral limbs (Schunk, 1988).

Conjugated eye movements require coordination of three cranial nerves and respective muscles. The afferent input to these cranial nerves is conveyed via the medial longitudinal fasciculus (MLF, within the centre of the brainstem), from the vestibular nuclei to the nuclei of the cranial nerves III, IV and VI. Thus, lesions affecting these anatomical areas may lead to different signs, mostly characterized by abnormal nystagmus (Lorenz *et al*, 2011).

The simultaneous impairment of these areas can lead to abnormal nystagmus, while the eye globe remains in central position (with no strabismus). However, lesions affecting the MLF may induce an absence of eye movements while moving the head, or even deconjugate movements of the eyes (which is known as external ophthalmoplegia or extraocular musculature paralysation). External ophthalmoplegia may also occur in lesions involving the nuclei of the cranial nerves III, IV and VI, their nerves and relative extraocular musculature. A similar condition, affecting the referred cranial nerves and sensory and autonomic function of ocular structures, can occur when the cavernous sinus is impaired (venous sinus housed in the middle cranial fossa, and adjacent to CN III, IV and VI) producing the *Cavernous sinus syndrome* (Lorenz *et al*, 2011).

Nystagmus consists of rhythmic involuntary eye movements. It can be physiologic and may be induced by visual or vestibular input. Both visual and vestibular are known as *jerk nystagmus* once they are composed by a first slow phase to one side, followed by a fast eye movement to the opposite side (which name the nystagmus direction) (Lorenz *et al*, 2011). Nystagmus is not pathognomonic for any disease or syndrome (LeCouteur, 2003).

The abnormal nystagmus is named after the direction of the movement. It may occur horizontal, vertical or rotatory nystagmus. Both horizontal and rotatory nystagmus (without direction alteration while moving the head at any position) are common in peripheral vestibular disorder. Vertical nystagmus and nystagmus changing direction of

the fast phase, while altering head position are common in central vestibular disorders, specifically in lesions affecting the brainstem and the *Flocculonodular Lobe* (Lorenz *et al*, 2011).

It is also reported a different kind of nystagmus, the *pendular nystagmus*, without fast or slow pattern, consisting only of smooth oscillations of eye position, mainly during gaze fixation. *Pendular nystagmus* is common in cerebellar disease or in some congenital visual deficits (Lorenz *et al*, 2011).

Strabismus is an abnormal position of the eye, and is common in vestibular disease (in both dogs and cats). Frequently occurs ventral or lateral deviation of the eye on the affected side (ipsilateral to the lesion), and it may be positional (while rotating the head dorsally) or spontaneous (permanent). For a correct neurological evaluation, both eyes must be simultaneously observed. The imbalance on bilateral vestibular input described above is also in the origin of that condition (Dewey & Costa, 2016).

Ataxia comprises the incapacity to accomplish coordinated motor activity, usually leading to an abnormal gait. Ataxia is not related with musculoskeletal impairment, weakness or abnormal movements, as tremor. This incapacity can be divided into three types, *sensory* or *proprioceptive*, *cerebellar* and *vestibular* Ataxia (Dewey & Costa, 2016).

Sensory or *proprioceptive* ataxia occurs because of unconscious proprioceptive pathways impairment (white matter of spinal cord), interrupting the respective ascending tracts, which is responsible by the absence or lack of sense of the limbs and body position. This type of ataxia is marked by incoordination and clumsy motor function, producing a swaying gait with wide-based stance. Affected limbs may present a longer stride and some animals can even drag the toes while walking. It is commonly associated with paresis (Dewey & Costa, 2016).

Cerebellar ataxia is induced by cerebellar disease, or lesions of the spinocerebellar tracts, affecting the regulation of movement rate and range. Animals usually exhibit dysmetria (commonly with a hypermetric pattern, marked by an overstepping gait with longer stride, usually seen in dogs) (Dewey & Costa, 2016).

Vestibular ataxia is caused by vestibular dysfunction. In unilateral lesions, animals may lean or fall to one side, while in bilateral disease they may exhibit a crouched position, with a marked side-to-side swaying of the head (Dewey & Costa, 2016).

Patients with concurrent facial paralysis and Horner's syndrome should be investigated for additional non-vestibular causes, as *otitis media* (Lowrie, 2012b).

Although Horner's Syndrome is not directly related with peripheral vestibular disease, the anatomical proximity between the oculosympatethic path and the petrosal temporal bone may lead to concurrent Horner's Syndrome in vestibular lesions (Garosi *et al,* 2012).

Facial paralysis can also coexist in vestibulocochlear nerve lesions due to facial nerve (VII) impairment, which exits the brainstem and courses by the facial canal, into the inner ear, in close relation with the vestibulocochlear nerve (VIII) (Lorenz *et al,* 2011; Jeandel *et al*, 2016).

Central vestibular disorders can display trigeminal nerve (V) dysfunction due to brainstem impairment (Lahunta & Glass, 2009; Penderis, 2003a; Penderis, 2003b).

Also, the abducent nerve (VI) may be injured in central vestibular disorders due to the commitment of some of the vestibular projections crossing the medial longitudinal fasciculus. However, isolated abducent nerve injuries are rare and are usually simultaneous with oculomotor nerve (III) injury since they are both involved in eye ball movement (Lowrie, 2012a; Penderis, 2003a). VI lesion may lead to medial strabismus (since it supplies the Lateral Rectus and Retractor Bulbi muscles) (Penderis, 2003a).

CN III to XII emerge from the medulla in different regions at the level of the brainstem, but only CN V, VI, VII, IX, X and XII may lead to central vestibular disorder, since their path intertwines with central vestibular paths described above (Lorenz *et al*, 2011).

Central vestibular disorder may lead to ipsilateral or contralateral (UMN) paresis, since the brainstem vestibular nuclei is anatomically close to the UMN brainstem nuclei (Platt & Garosi, 2012; Hahn & Thomson, 2012)

2.4.1. Differences between central and peripheral vestibular disorder

The exhibited neurological signs in vestibular disease can differ according to the lesion' origin. Central and peripheral diseases can lead to different displays.

Table 2 - Main clinical signs exhibited in central (CVD), peripheral (PVD) or paradoxical central vestibular disease (paradoxical CVD) (Lorenz *et al*, 2011; Schunk, 1988; Lahunta & Glass, 2009).

Signs	CVD	PVD	Paradoxical CVD
Head tilt	Yes	Yes	Possible but rare, toward the opposite side of the lesion
Nystagmus	Yes, it is possible to present every nystagmus types and directions (horizontal, vertical, rotatory, positional/non-positional, conjugate and deconjugate)	Yes, although it is not possible to occur vertical, positional and deconjugate nystagmus	Yes, with the fast component toward the side of the lesion
Strabismus	Yes	Yes	Yes
Ataxia (asymmetrical, with propensity to fall or lean to one side)	Yes, vestibular and cerebellar ataxia	Yes, vestibular ataxia (leaning, falling and circling)	Yes, cerebellar and vestibular ataxia (propensity to fall, lean and circle to the opposite side of the lesion)
Circling	Yes (to one side)	Yes (to one side)	Possible but rare, to the opposite direction of the lesion
CN deficits	Yes, CN V, VI, VII, IX, X and XII may be involved	CN VII (in middle ear involvement), VIII. Possible Horner's Syndrome	Possible, such as CN V and VII deficits (unilateral deficits, corresponding with the side of the lesions)
Cerebellar signs	Possible	No	Yes
Horner's Syndrome	No	Yes	No
Mental status	Disoriented; some degrees of depression are possible	Alert, some animal can present some degrees of disorientation	Disoriented; some degrees of depression are possible
Paresis	Possible (ipsilateral	No	Possible (ipsilateral paresis)

	hemiparesis or tetraparesis in paradoxical vestibular disorder)		
Proprioceptive deficits	Possible	No	Some postural deficits are possible
Autonomic signs (Emesis)	Yes	Yes	Yes

2.5. Possible pathophysiologic causes of neurological dysfunction of vestibular apparatus

Regarding the DAMNIT-V mnemonic of differential diagnosis, table 3 resumes the main possible pathophysiologic causes for vestibular disorder (Gough, 2007).

Table 3 - Main pathophysiologic causes for vestibular disorder, and its associated central or peripheral vestibular pathologies (Schunk, 1988; Lowrie, 2012b; Kent *et al*, 2010; Flegel, 2014; Vernau & LeCouteur, 1999; Rossmeisl, 2010; Lorenz *et al*, 2011)

Pathophysiologic causes		Diseases/ disorders	
		CENTRAL DISEASE	PERIPHERAL DISEASE
Degenerative		Cerebellar abiotrophies Storage disorders (*GM_1* and *GM_2 gangliosidosis*, *sphyngomyelinosis*, *mannosidosis*, *glucocerebrosidosis* and *globoid cell leukodystrophy*)	Non-reported
Anomalous (congenital)		Hydrocephalus Cystic malformation (intra-arachnoid, Dermoid and Epidermoid), Caudal Occipital malformation	Congenital Vestibular disease (*Akita Inu*, *Beagle*, *Cocker Spaniel*, *German Shepherd*, *Doberman*, *Tibetan Terrier*)
Metabolic		Hypothyroidism (rare; dogs)	Hypothyroidism (dogs)
N	Neoplastic	Primary and metastatic caudal fossa tumours (Meningioma, Oligodendroglioma, Medulloblastoma, Lymphoma, choroid plexus tumours)	Peripheral nerve and medial/inner ear tumour; squamous cell tumour, fibrosarcoma, osteosarcoma, ceruminous and sebaceous gland adenocarcinoma
	Nutritional	Thiamine deficiency	Non-reported
I	Inflammatory	Meningoencephalitis (unknown origin) (e.g. granulomatous; dogs)	Nasopharyngeal polyps (in cats), Neuritis of

			the vestibulocochlear nerve
	Infectious	Infectious encephalitis due to Canine distemper, *Toxoplasma* spp., *Neospora* spp., *Erlichiosis, Rocky mountain fever, Bartonella* spp., aberrant parasite migration (*Cuterebra* spp.; in cats) bacteria (*Staphylococcus* sp., *Pasteurella* sp.), FIP and fungus (*Cryptococcus, Blastomycosis*)	Otitis *media/interna*
	Immune-mediated	Non-reported	Non-reported
	Iatrogenic/toxic	Metronidazole and Lead toxicosis	Bulla osteotomy, fracture or haemorrhage Ototoxicity: topical/systemic Aminoglycosides with concurrent application of diuretics, such as furosemide and chemotherapeutic drugs like, cisplatin or nitrogen mustard drugs; topical Chlorohexidine (and other antiseptics), topical fipronil (10% solution), propilenoglycol. Frequent ear flushing (including Cerumenolytic agents)
	Idiopathic	Non-reported	**Idiopathic vestibular disease** (idiopathic benign vestibular disease in dogs and feline idiopathic vestibular neuropathy); Polyneuropathy involving the CN VII and VIII (unknown origin, reported in dogs)
T	Traumatic	Head trauma (Brainstem)	Head trauma (Inner ear)
Vascular		Brain infarct and haemorrhage Feline ischemic encephalopathy	Non-reported

2.6. Idiopathic vestibular disease

Vestibular disorders with idiopathic origin include idiopathic vestibular disease (known as idiopathic benign vestibular disease in dogs and feline vestibular idiopathic neuropathy in cats), and polyneuropathy (involving the CN VII and VIII) which is rare and only reported in dogs (Lowrie, 2012b).

Idiopathic vestibular disease is usually manifested unilaterally, and may occur in both cats and dogs with similar onset and presentation, despite exhibiting tenuous disparities between these species (Lowrie, 2012b; Schunk, 1988). It often occurs in geriatric canine patients (twelve and a half years is the mean age of onset, but it is tendentiously more common in dogs over ten years) (Flegel, 2014), may also be named in dogs as *old dog vestibular disease* or *geriatric vestibular disease*. There is no breed or sex predilection (Lowrie, 2012b; Schunk, 1988).

On the other hand, the age of vestibular disease onset in cats is not specific, although it is commonly seen in young adult cats. It is reported to often occur in outdoor cats (with higher incidence) (Rossmeisl, 2010), from late spring to early fall in north-eastern United States. This specific seasonal onset may be related with *Cuterebra* Larval migration. As in dogs, there is no breed or sex predilection (Lowrie, 2012b; Bagley, 1997).

Idiopathic neuropathy is a similar condition to Idiopathic vestibular disease, involving the vestibular nerve. The clinical signs are similar, but their remission may persist for several weeks, regardless of the instituted medication (Bagley, 1997).

2.6.1. Clinical signs

In both cats and dogs the clinical signs have an acute and severe onset (Bagley, 1997). Those clinical signs have origin from the peripheral vestibular apparatus (Bagley, 1997).

The idiopathic vestibular signs usually include *head tilt* (toward the side of the lesion), asymmetric rolling, circling, leaning or falling (vestibular ataxia, while strength is preserved) and positional strabismus or spontaneous/positional nystagmus (only horizontal and rotatory). Blindfolding an animal with subtle vestibular signs may exacerbate the signs, mainly the *head tilt* and *circling* (LeCouteur, 2003).

Initially, animals tend to be so incapacitated that are unable to stand and proceed a normal gait and it is usually misdiagnosed as a cerebrovascular accident; the neurological

examination may also be difficult to perform, especially in cats. Those signs, despite of being initially severe, are restricted to the vestibular system (Dewey & Costa, 2016; Bagley, 1997; Negrin *et al*, 2010; Schunk, 1988). The concurrent presentation of Horner's Syndrome and facial nerve paralysis is also reported, but other causes should be investigated (e.g. frequent sequelae of Otitis media) (Negrin *et al*, 2010; Schunk, 1988).

In peripheral vestibular disease nystagmus does not change in direction with different head positions (LeCouteur, 2003).

Animals usually fall while attempting to shake their head, and may walk along a wall for additional support (Schunk, 1988). Usually the vestibular ataxia is initially more pronounced in the thoracic limbs, progressing after to the pelvic limbs (LeCouteur, 2003). Initially the affected animals may compensate the vestibular disorder resorting to vision (LeCouteur, 2003; Schunk, 1988).

Additionally, animals with idiopathic vestibular disorder do not exhibit depressed mentation, although it may seem to be mentally depressed which is possibly justified by pain or disorientation (Negrin *et al*, 2010). Cats use to be reluctant to move and cry continuously (Chrisman, 1980).

Proprioceptive and cranial nerve deficits (beyond VII and VIII) are not present since it indicates the central vestibular system involvement, although delayed to absent *Righting Response* may occur (Negrin *et al*, 2010; Schunk, 1988). Cats with vestibular disorder may exhibit wide-based stance (LeCouteur, 2003).

Some animals may present emesis or nausea on the first stages of peripheral vestibular disease with acute onset (LeCouteur, 2003; Schunk, 1988).Vomiting is more common in dogs whilst it is relatively rare in cats (Schunk, 1988).

The typical clinical signs of Feline Idiopathic vestibular disease may establish within 72 hours and are often preceded or simultaneous to upper respiratory tract disease (LeCouteur, 2003). The expected recovery period is about two to four weeks (usually complete recovery; prognosis details will be further described) (Vernau & LeCouteur, 1999).

It is not expected that the patient exhibit simultaneously all the clinical signs mentioned and as some signs are transient, some may be absent while proceeding to the physical/neurological examination (LeCouteur & Vernau, 1999).

2.6.2. Ancillary diagnostics tests and respective findings

A detailed retrospective animal clinical data should be collected. It is also very important to proceed to a complete neurologic examination to understand the origin of the actual vestibular dysfunction (if it is from the central or peripheral Vestibular apparatus) or even find a specific neurolocation (Rossmeisl, 2010).

The diagnosis of idiopathic vestibular disease is based on clinical signs and exclusion of other differential diagnosis or causes (Thomas, 2000).

Ear evaluation is important due to the proximity of the peripheral vestibular apparatus to the petrosal portion of temporal bone (whitin the ear is located) (Lahunta & Glass, 2009). Each ear must be primarily observed macroscopically, followed by otoscopic examination in order to find any signs of inflammation or infection (e.g. otitis media) or any mass presence (e.g. polyps) and verify the integrity of the tympanic membrane; it may also be collected samples for further cytology and AST, infection is suspected (Thomas, 2000). If tympanic bulla lesion is a suspicion it may be evaluated by radiographic imaging (animal with his mouth open and various projections may be performed – dorsoventral, lateral obliquus and rostroventral-caudodorsal projections) (Thomas, 2000). If a more precise evaluation is needed, myringotomy (tympanic membrane incision) may be an option, despite of being invasive, but it may help searching for middle or inner ear disease (e.g. infection, inflammation, neoplasia) and even can be performed biopsy for further histology (Thomas, 2000).

It is important to perform a complete blood cell count, ionogram, serum biochemistry, and urinalysis. A thyroid function evaluation should also be performed, including the evaluation of T4, free T4, TT4 and TSH (Webb *et al*, 2009). Since the idiopathic vestibular disorder signs are often misdiagnosed as cerebral vascular accidents, the evaluation of serum cholesterol and fibrine D-dimers may also be helpful to exclude that suspicion (Platt & Garosi, 2012).

Both CT and MRI may be performed to evaluate the presence of lesions at the peripheral vestibular paths described behind (any lesion involving the vestibular division of CN VIII, specifically the receptor organs and peripheral axons) (Chrisman, 1980). MRI is more specific for the evaluation of soft tissues and it contrasts, whereby it may be a better option for detecting these kind of lesions, especially when a contrast agent, such as gadolinium, is administered (Thrall, 2013). The CSF analysis is only justifiable when

GME or bacterial meningitis are suspected, since it is expected to detect neutrophilia and an increase in TP whilst in the CSF (Chrisman, 1980). Bacterial culture may be performed, but is only efficient if the infection is severe (Chrisman, 1980).

Pharynx palpation should also be performed to detect inflammation signs (inflammation that may ascend via auditive tube into the inner and middle ear) (Chrisman, 1980).

If congenital vestibular disease is suspected (with associated loss of hearing) it may be performed a BAER test, which allows to evaluate the origin of deafness (Rossmeisl, 2010). This test allows characterizes the deafness as Conductive or Sensorineural, once it depends, respectively, on mechanical transducing mechanisms on external and inner ear cavities and neural mechanisms in the peripheral nerve, brainstem and inner ear (Cole, 2009).

The EEG analysis may not be helpful since the peripheral vestibular disorders do not lead to seizures, thus it is not expected to observe abnormalities on the encephalic electric activity (Chrisman, 1980).

The normal values or results on these exams, excluding other diseases or causes, and the progression of clinical signs are a criterion to classify the vestibular disease as idiopathic (Thomas, 2000).

2.6.3. Differential diagnosis

Idiopathic Vestibular disease is often misdiagnosed with Cerebrovascular accidents or TIA, due to the acute onset and severity of early signs (the TIA have an earlier onset and resolves within twenty-four hours) (Lowrie, 2012b). Since it is not a lesion based in the peripheral vestibular apparatus, a complete neurological examination should be performed, in order to better localise the lesion. If any doubt about the lesion origin remains, the evaluation of, hyperadrenocorticism, hypertension, hypothyroidism, cardiac and renal disease, seric cholesterol and fibrine D-dimers should be performed (Lowrie, 2012b).

The main differential diagnosis for Idiopathic Vestibular disease are idiopathic polyneuropathy involving CN VII and VIII (only reported in dogs and in case no other cause is defined), Hypothyroidism (common differential diagnosis in dogs); Congenital vestibular disease; Peripheral nerve and middle/inner ear tumour, squamous cell tumour, fibrosarcoma, osteosarcoma, ceruminous and sebaceous gland adenocarcinoma;

Nasopharyngeal polyps (in cats), Neuritis of the vestibulocochlear nerve; Otitis media/interna; head trauma (lesion involving the inner ear). (Lowrie, 2012b; Kent *et al*, 2010; Flegel, 2014; Vernau & LeCouteur, 1999; Rossmeisl, 2010; Lorenz *et al*, 2011)

Iatrogenic origins should also be considered, such as bulla osteotomy, fracture or haemorrhage; Ototoxicity (topical/systemic aminoglycosides with concurrent application of systemic furosemide and chemotherapeutic drugs like, cisplatin or nitrogen mustard drugs; topical Chlorohexidine, topical fipronil (10% solution)); Frequent ear flushing (Lowrie, 2012b; Kent *et al*, 2010; Flegel, 2014; Vernau & LeCouteur, 1999; Rossmeisl, 2010; Lorenz *et al*,2011).

2.6.4. Treatment

There is no known treatment for this specific disorder. Steroid and Nonsteroidal Anti-inflammatories, as well as antihistamine motion sickness drugs, had not proven to be helpful in disease progression (Rossmeisl, 2010). The use of antibiotic therapy is controversial and diverges. However, the empirical use of a large-broad antibiotic may be useful to treat eventual occult otitis media /interna (Rossmeisl, 2010).

Thus, the therapy is mainly supportive. In this disorder it may help administrate anti-emetics for eventual occurring nausea and vomiting (in the first stages of the disease), as well as, anxiolytic drugs, such as *diazepam*, as the loss of balance and equilibrium may lead to stress and anxiety (Rossmeisl, 2010). Since the nausea and vomiting are usually transitory (from twenty four to thirty six hours after the clinical signs onset) usually antiemetic or antimotion drugs are not necessary (Schunk, 1988).

Some authors consider beneficial the administration of intravenous drugs in dogs such as propentofylline (responsible for blood flow enhancement) (Flegel, 2014).

It is reported the practice of physiotherapeutic exercises do decrease the vertigo sensation on dogs, although it is not deeply investigated in veterinary medicine and is based on physiotherapeutic modalities used in humans with Benign Paroxysmal Positional Vertigo (BPPV) (the aim of this modality is reposing the otoliths disposition along the semi-circular canals) (Kraeling, 2014).

2.6.5. Prognosis

The prognosis of this disorder is considered good to excellent. In dogs the signs improve in a few days (commonly reducing abnormal nystagmus is the first sign of improvement) and the full (or almost complete) remission of clinical signs happens after two to four weeks after the initial onset (Flegel, 2014; Thomas, 2000). In some dogs may persist a mild *head tilt* and disequilibrium (often when doing sudden head movements, like shaking the head) (Flegel, 2014; Thomas, 2000).

The expected recovery period in cats is about two to four weeks (Vernau & LeCouteur, 1999; Thomas, 2000). A mild *head tilt* and ataxia may persist in some cases, but it is not common (Thomas, 2000; Vernau & LeCouteur, 1999). Nystagmus usually resolves within seventy-two hours, although positional nystagmus may be elicited. Also in seventy-two hours the animals start to recover the gait (are ambulatory) (Chrisman, 1980).

Recurrence is not common in both species, but it may occur in the same or contralateral side (Schunk, 1988).

3. Aims

Analyse and compare the results of the neurological examinations and the respective ancillary diagnostic exams with the disease progression and prognosis of each animal suspected with idiopathic vestibular disorder.

4. Materials and Methods

During the internship, it was performed a retrospective search in the database of the Clínica de Referência Veterinária (RRV) of all animals suspected of having vestibular disease, during the period between 2011 and 2017. The inclusion criteria were animals with neurologic examination compatible with possible vestibular disease, animals that were submitted to complete neurological examination, to MRI/CT (with or without CSF collection and analysis), to a basic or complete blood cell count and biochemical serum analysis (including thyroid function evaluation).

4.1. Study sample analysis

In the clinic database it was possible to collect 19 animals in which idiopathic vestibular disease was suspected (17 dogs and 2 cats).

4.2. Sample analysis and characterization

In the clinic database it was possible to collect twenty animals in which idiopathic vestibular disease was suspected (seventeen dogs and two cats).

From the twenty analysed animals, only nine were included on this study. The exclusion of animals from this sample was due to an absence of a complete neurological examination compatible with vestibular disease, MRI/CT imaging, a basic or complete blood analysis. This sample is composed by seven dogs and two cats

The canine sample include animals with ages ranging from four to sixteen years, four male and three female individuals. The dog breeds include one *Cocker Spaniel*, one *Epagneul Bretton*, one *Golden Retriever*, one *Portuguese Perdigueiro*, one *Yorkshire Terrier* and two mixed breed dogs.

The feline sample include two mixed breed spayed queens with seven and eighteen years old.

5. MRI Protocol

The MRI images were obtained by a Vet-MR® ESAOTE 0,2T equipment. When contrast administration was required, the paramagnetic contrast Gadolinium (Dotarem® Laboratórios Guerbet®), in a dose of 0.2 ml per kilogram, was administrated intravenously (IV). In all the MRI exams, it was obtained MRI images in dorsal, sagittal and transversal plane, resorting the T1W, T2W, FLAIR and STIR sequences before the contrast administration, and T1W after it administration. When needed it was used three-dimensional reconstructions or additional MRI sequences.

The obtained images were evaluated to detect the existence of possible vestibular apparatus lesions, or lesions leading to vestibular disorders (focusing on the CN VII, VIII, brainstem, cerebellum, prosencephalic area, and middle or inner ear).

In cases in which inflammatory or infectious disease was suspected, it was also collected CSF from cisterna magna, for posterior analysis, or for antibiotic sensibility test if infectious process was suspected.

6. Results

From a data base of 20 animals suspected of possible vestibular disease, nine animals (seven dogs and two cats) were selected for description, according to the inclusion criteria described in the previous section.

Each case will be described individually, and specific considerations will be written for each clinical situation. Only the physiological, anatomical or neurologic parameters outside normal range values will be referred in the text.

6.1. CASE 1

6.1.1. Animal demographics and anamnesis

A neutered *Epagneul Bretton* bitch with 16 years old, weighting 17.05 kg, was rerredfor neurological appointment at RRV at January 12th of 2017, after presenting clinical signs compatible with vestibular disease since December 23rd of 2016. There was no evidence of trauma.

In December 23rd, she started presenting circling (to the right side), with tendency to fall to the left side. The animal was hospitalised on the same day, and medicated with metilprednisolone (*Solu-medrol*®) At December 28th, she was submitted to CT Scan in FMV-UL, which had not revealed any evident alterations. Prednisolone (*Lepicortinolo*®) was stopped two days after during hospitalization, because of nausea and vomiting. She had shown some improvements in the clinical signs since the beginning of the treatment until 12th January, despite of being unable to walk or stand. She was also taking Vitaminic complexes (A, B and D) and Omega 3 fatty acids (*Conecta*®), Metoclopramide 0.4mg/kg q6h, *per os* (*Primperan*®), Propentofylline (*Karsivan*®) and Citicoline (*Somazina*®*)* since December. She had presented some improvements in the clinical signs till 12th January, despite of being unable to walk or stand.

6.1.2. Neurological appointment (12th January 2017) at RRV – neurological examination

The animal was presenting left vestibular ataxia, with marked cephalic inclination to the same side. The animal could stand and walk a few steps, but only supported (it was tending to fall or lean when the support was taken off).

It exhibited positional ventral strabismus on the left eye. It was not observed any postural alterations on the four limbs.

6.1.3. MRI report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

On the MRI images it was possible to detect small tenuous hyperintense signal on the periventricular white matter, on T2 and FLAIR sequences, and T2 signal avoid inside the mesencephalic aqueduct (suggesting brain vascular alterations, such as hypertension)

(figure 6 and 7). There were not any other neurocranial alterations, especially on the internal acoustic meatus (CN VII and VIII), and middle and inner ear (membranous labyrinth) before and after the paramagnetic contrast administration (Gadolinium).

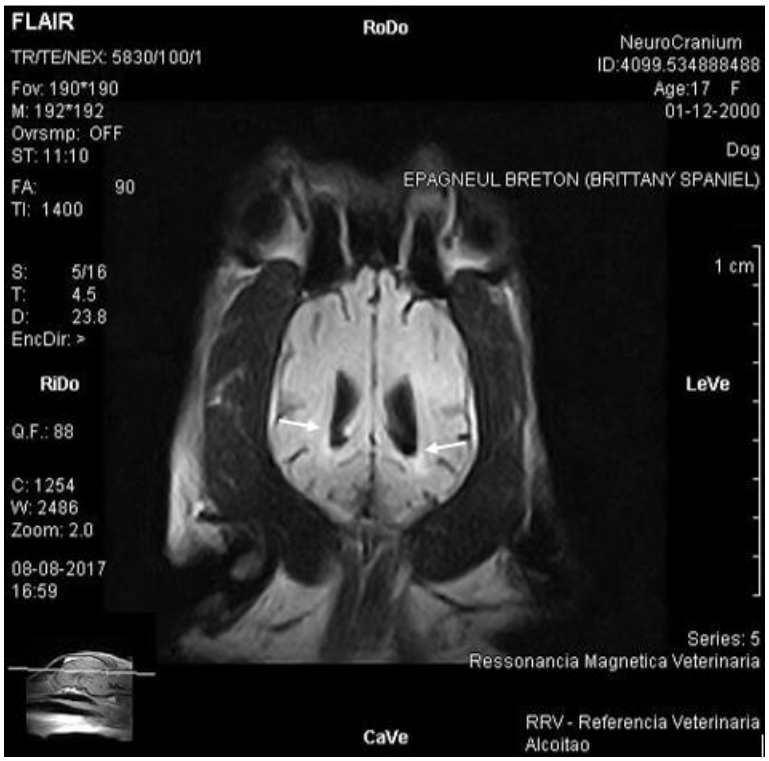

Figure 6 - FLAIR sequence (before the gadolinium administration) revealing bilateral signal hyperintensity on the margins of the lateral brain ventricles (white arrows). Image gently ceded by Dr. João Ribeiro from RRV.

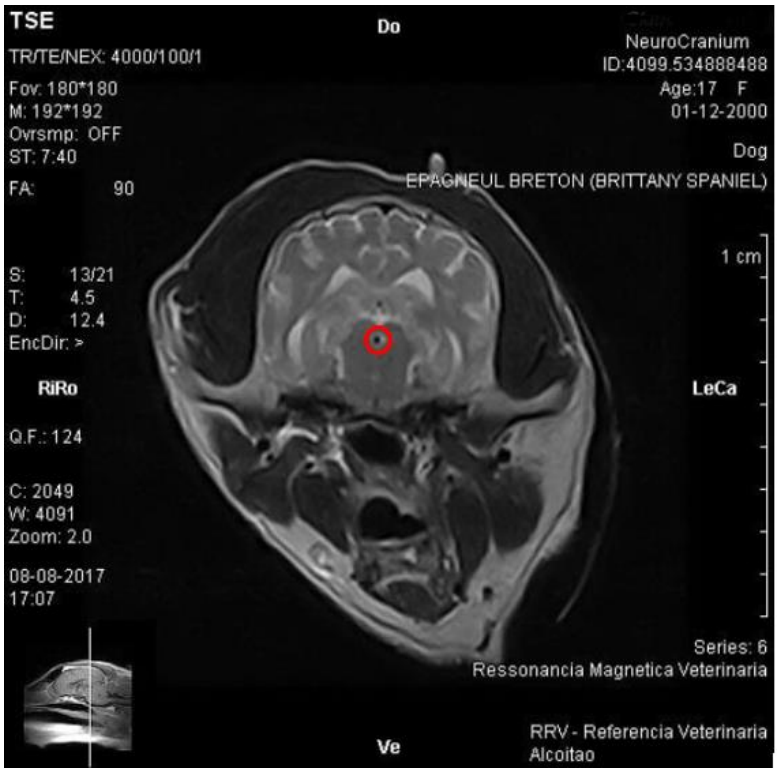

Figure 7 - T2 sequence revealling signal absence on the mesencephalic aqueduct (inside the red circle). Image gently ceded by Dr. João Ribeiro, from RRV.

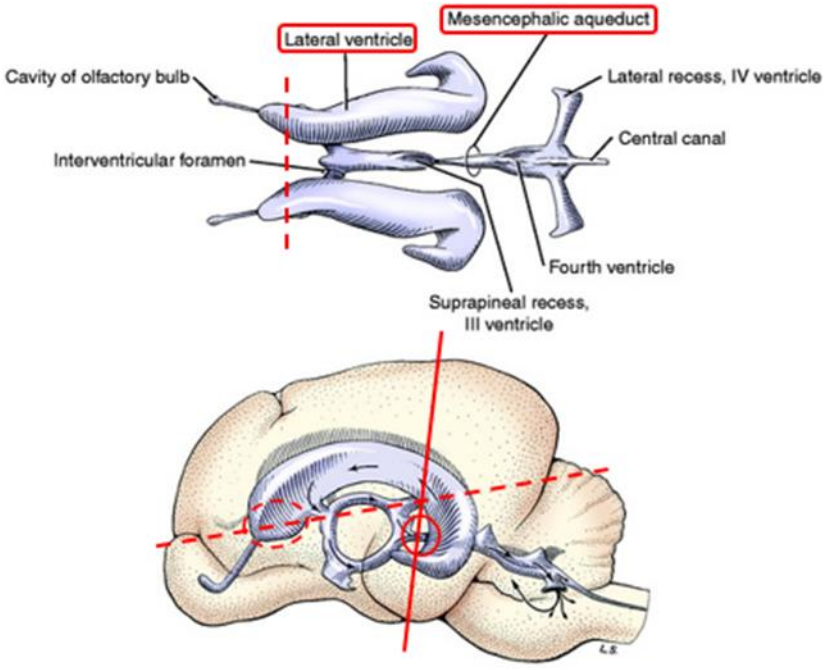

Figure 8 - The red continuous line represents the T2 sequence and the red circle the mesencephalic aqueduct, as shown on the previous image. The dashed red line and circle represent FLAIR sequence of both studied cut and the bilateral hyperintense area (lateral ventricles). (Adapted from Evans & Lahunta 2013)

6.1.4. Medical considerations/differential diagnosis

Towards the results of the MRI, the clinical signs were classified as being originated from the peripheral vestibular apparatus, suggesting an eventual idiopathic vestibular disease (regarding the animal data, history and neurological deficits) as well as vascular alterations (such as arterial hypertension or blood hyper viscosity) and metabolic diseases (like hypothyroidism or Hypercholesterolemia).

Additional exams were recommended: blood count, biochemical seric evaluation (including thyroid function), cardiovascular and ophthalmologic evaluation. It was suggested to complement the disease progression with adapted physiotherapy and the administration of anti-vertiginous drugs, such as Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day (*Betaserc®)* or Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day, to reduce the ataxia and disequilibrium (Brum *et al*, 2010; Nelson & Couto, 2014).

6.1.5. Disease Progression

Following three weeks of treatment, the animal showed improvements of some of the clinical signs.

However, the analytic evaluation had exhibited a mild ALT (143 U/l, ranging between 13-83U/l, *Fuji DRI-CHEM*®) and ALP (351 U/I, ranging between 17-76 U/l, *Fuji DRI-CHEM*®) increase and signs of Primary Hypotiroidism (TT4 11.70 nmol/l, ranging between 13.0-51.0 nmol/l, and TSH of 1.27 ng/ml, ranging between 0.03-0.6 ng/ml, *Indexx*®) since it presented a simultaneous decrease of TT4 seric value and an increase of TSH seric value. The alteration of thyroid parameters may be one of the causes leading to vestibular signs.

Central vestibular signs were exhibited a few months after the first clinical onset and the animal was submitted to a second MRI examination revealing increased severity of the previously changes, i.e. hyperintense signal on the periventricular white matter and aqueductal T2 signal avoid, suggesting a vascular process similar in human Medicine, as *Vascular Dementia*, regarding the age of the animal as well as the persistent high values of SBP (a medium value of 140 mmHg) or possible Hypertensive Encephalopathy, reported in Veterinary Medicine (O'Neill *et al*, 2013). This vascular process might be worsened by the primary hypothyroidism

6.2. CASE 2

6.2.1. Animal demographics and anamnesis

A mixed breed non-neutered male dog with fourteen years old, weighting 30 kg, was referenced for neurological appointment at RRV at October 24th, 2012. It has been showing walking difficulties during the past two years, that were attributed to joint impairment. The dog had been medicated with NSAID's (which ones were not reported) since the clinical signs onset. On 20th October 2012, before the RRV neurological appointment, according to the dog's tutors, it exhibited tremors associated with defecation, urination and emesis, that lasted about 15 to 30 minutes, but the mentation remained unaltered. In that day, the dog was hospitalized for one night in another clinical facility, where it received IV NaCl 0,9% fluid therapy, and started phenobarbital 75 mg (*Bialminal*®) twice a day, Firocoxib 227mg, one pill, once a day (*Previcox*®, indicated to administrate for ten days). This dog regularly took analgesic drugs for joint pain. After clinical discharge, the animal was remaining prostrated, despite of eating and being alert. It was unable to stand and walk, and had urination control, despite of urinating in lateral recumbence.

Before that episode it was only noted a mild corneal opacity on the right eye. There was no evidence of trauma.

The patient was previously submitted to BAER test and it had shown inactivity of the Cochlear portion of the Vestibulocochlear nerve.

6.2.2. Neurological Appointment (24th October 2012) at RRV– neurological examination

The patient was non-ambulatory and mildly depressed. On neurologic examination, postural reactions were slightly decreased at the left side, and, although difficult to evaluate at the right side, postural reactions were also decreased.

At the cranial examination, the patient had positional ventral strabismus and absent response to menace test at the right eye, although it had right eye corneal opacity. The menace test was positive on the left side, and no evidence of nystagmus was observed. The patient tended to exhibit head tilt (to the right side). It was also performed a Schirmer test (9mm at the left eye and 0 mm at the right eye).

6.2.3. MRI report

It was performed T1W, T2W, STIR and FLAIR sequences of the neurocranium before the IV paramagnetic contrast administration (Gadolinium) and T1W, FLAIR and 3D-T1W after it administration.

The MRI exam did not reveal any morphologic lesions or evident signal alterations, before and after contrast administration. The middle/inner ear and vestibulocochlear nerves had not evident alterations.

Analysis of CSF, collected from *Cisterna magna* was within normal range parameters, and it was negative for *Pandy's Reaction test* (used to detect the elevated levels of proteins, mainly globulins).

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.2.4. Medical considerations/differential diagnosis

The absence of alterations on the neurocranium may suggest the presence of an idiopathic vestibular disease. The mobility difficulties may probably be originated by orthopedic impairment (previously diagnosed) and not by neurological causes.

Differential diagnosis includes metabolic causes (such as hypothyroidism, kidney, liver or electrolytic dysfunction), paraneoplastic process or vascular lesions (micro infarctions, non-detectable on low field MRI equipment)

It was suggested the evaluation of thyroid function (TT4 and TSH), ionogram, reevaluate the kidney function, and investigate possible neoplastic process (through abdominal ultrasound). It was recommended to stop the anti-epileptic medication, evaluate the orthopedic function (acting specifically on the orthopedic pain), avoiding any drugs or doses that might produce sedation, because of the risk of accentuating the ataxia.

It was, also, suggested the implementation of an adequate physiotherapy plan to help controlling the orthopedic problems, as well as the administration of anti-vertiginous drugs, such as Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day (Brum *et al*, 2010).

6.2.5. Disease progression

The patient presented a remission of the clinical signs through the following three to four weeks.

It was submitted to blood analysis a few days after the appointment, which revealed a slight increase of ALT, Creatinine and BUN levels and diminished levels of serum TT4, but with normal TSH value, demonstrating a possible transitory secondary hypothyroidism, probably due to the administrated medication, such as the Phenobarbital, which increases Thyroid hormone elimination, decreasing the measured serum total and free thyroid hormone and increasing the serum thyroid-stimulating hormone concentration) (Nelson & Couto, 2014).

6.3. CASE 3

6.3.1. Animal demographics and anamnesis

A male, mixed breed and non-neutered large dog, with 10 years old, weighting 23.1 kg was referenced for neurological appointment at RRV at October 13th, 2011, after presenting clinical signs of vestibular disease with acute onset, such as head tilt and disequilibrium, while standing and walking. The animal was not taking any medication and there was no evidence of trauma.

6.3.2. The neurological appointment (13th October 2011) at RRV– neurological examination

Whilst performing the neurological examination, it was possible to detect a mild vestibular ataxia (disequilibrium, tending to lean to the right side as well as presenting a slight trunk curvature to the same side), while standing or walking. The neurocranium examination had detected *head tilt* (to right side), positional ventral strabismus on the right eye, horizontal nystagmus (with the fast phase to the left side, unaltered by changing the head position). No other significant changes were observed.

6.3.3. MRI report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration. No morphologic lesions nor inflammatory, vascular or neoplastic disease were observed. The middle/inner ear and vestibulocochlear nerves had not evident alterations.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.3.4. Medical considerations/ differential diagnosis

The results of the neurological examination, clinical signs and the acute onset, and the MRI results indicate a possible peripheral vestibular disorder, suggesting an idiopathic vestibular disease. Others differential diagnosis must be considered, such as hypothyroidism, kidney, liver or electrolytic dysfunction, hypertension, paraneoplastic process or vascular lesions (micro infarctions or TIA, non-detectable on low field MRI equipment).

Additional exams were recommended, such as a complete blood count and biochemical serum analysis (thyroid, liver and kidney function, ionogram), systolic blood pressure measurements, and abdominal ultrasound for discarding possible neoplastic pathologies. It was also suggested the administration of symptomatic medication, such as anti-emetics or anti-vertiginous drugs (like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Maropitant 2mg/kg, *per os*, once a day or Meclizine, 25mg per dog or 4mg/kg, *per os*, once a day) in order to reduce nausea and vestibular ataxia (Brum *et al*, 2010).

6.3.5. Disease progression

Results of the ancillary tests just showed alterations on the fibrine D-dimers serum value, which was slightly increased (1.12 µg/L; maximum reference value is 0.25 µg/L), which may suggest an isolated TIA or micro-vascular process, non-detectable on low-field MRI, as the possible cause of this clinical onset.

Four weeks after the clinical onset of the disease, the patient presented almost total remission of the clinical signs within three to four weeks, although a mild head tilt had remained.

The SBP measurement was performed, but it presented healthy and normal values.

6.4. CASE 4

6.4.1. Animal demographics and anamnesis

A sterilized Golden Retriever bitch with twelve years old, weighting 29.9 kg, was referenced for neurological appointment at RRV August 8th, 2016.

Three months earlier, the patient presented an acute episode in which she was unable to walk and stand, apparently without associated pain. Radiographic examinations at that time showed no evident alterations. The patient presented total remission of these signs two days after the clinical onset, without taking any medication.

In June, it had also presented some mobility difficulties, associated with disequilibrium and nystagmus (as described by other veterinary clinic), but the clinical signs totally disappeared also after two days. It performed a CT scan (without CSF collection) on FMV-UL on June15th, 2016 (revealing a slight mineralization of the auditive conducts).

On August 3rd, 2016, it had presented similar clinical signs with acute onset, described by the clinic as consisting on acute disequilibrium, horizontal nystagmus (but only on the right side), and loss of appetites. The patient had not recovered so fast from this episode (as usual) and started having diarrhea. It was not instituted any medication and there was no evidence of trauma.

A sterilized Golden Retriever Bitch with twelve years old, was presented for neurological appointment at 8th August 2016.

6.4.2. Neurological appointment (8th August 2016) at RRV– neurological examination

The animal was alert (despite of being slightly nervous). It presented head tilt (to the left side) with a slight vestibular ataxia (to the same side). The postural reactions were a slightly decreased on the left biped, despite of being present.

Whilst evaluating the neurocranium it was possible to detect positional ventral strabismus on the left eye, without any nystagmus. Any other deficits were detected.

6.4.3. MRI report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

The neurocranium MRI presented symmetrical, without any deviations from de medial line or space occupying lesions. The ventricular system was symmetrical and the sign differentiation between the brain white and grey matter was considered normal. It was not observed any significant sign alterations or highlights after contrast (gadolinium) administration.

The tympanic bullas were normal, and the inner ear, vestibulocochlear and facial nerves were also with normal diameter, and had not any evident sign alterations before and after the contrast administration.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.4.4. Medical considerations/differential diagnosis

The clinical signs were characterized by intermittent vestibular episodes (with acute onset) without any significant image alteration. The differential diagnosis was vascular disease, such as micro infarctions, TIA, cardiovascular syncope, hypertension, blood hiperviscosity, toxic/metabolic disease (such as hypothyroidism) or paraneoplastic process, as well as idiopathic vestibular disease.

It was suggested a cardiovascular evaluation (including SBP measurements), blood analysis (including cholesterol, thyroid function, fibrine D-dimers), abdominal ultrasound (for detecting any neoplastic process) and thoracic radiography.

It was also suggested the administration of symptomatic medication, such as anti-emetics or anti-vertiginous drugs (like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day; Maropitant 2mg/kg, *per os*, once a day or Meclizine, 25mg per dog or 4mg/kg, *per os*, once a day) in order to reduce nausea and vestibular ataxia (Brum *et al*, 2010).

6.4.5. Disease progression

Blood analysis (including thyroid function and fibrine D-dimers evaluation) revealed normal thyroid values (TT4 and TSH), but the Fibrine D-dimers values were increased (0.55mg/L, whilst the normal values must be less than 0.40 mg/L; *DNAtech*), which may suggest vascular alterations with intermittent episodes, such as TIA, micro-infarctions, blood hyperviscosity.

It is plausible that this patient suffered from idiopathic vestibular disease, but the clinical signs pattern (intermittent and frequent episodes) is not common in this condition. Idiopathic Vestibular syndrome is usually characterized by a single onset (also with a brief remission) with rare cases of disease recurrence (Chrisman, 1980).

The clinical signs disappeared on the following three to four weeks (without any instituted medication), but it was not possible to follow the patient after that period, and it is possible that similar episodes had occurred.

6.5. CASE 5

6.5.1. Animal demographics and anamnesis

A mixed breed neutered bitch with thirteen years old, weighting 8.6 kg, was referenced for neurological appointment at RRV April 11th, 2016. This animal was adopted from a shelter, and suffered from canine distemper when it was young. It presented a full recovery at that time, despite of always having pendent tongue (pending outside the oral cavity), but with normal capacity of move and retract it.

Six months earlier, the patient started showing head tilt, and disequilibrium (to the right side) (possibly vestibular ataxia), but there was a spontaneous remission after a few days, with a remaining slight head tilt.

At April 8th, 2016, three days before the evaluation at RRV, the patient suddenly started presenting disequilibrium and disorientation, which disappeared a few minutes later (with no evidence of trauma). About two hours later started presenting oscillating movements of the head. The patient was hospitalized for one night at a veterinary hospital, in which it was clinically observed, and several ancillary diagnostic tests were performed. It was possible to detect a relevant vestibular ataxia, head tilt to the left side (with the tongue pending to the right side), horizontal nystagmus (fast phase direction was not described), and almost absent responses to pupilar reflex test on both eyes. The blood analysis revealed a slight increase of RDW (15.9%, ranging between 11 and 15.5%) and of ALT values (95 mg/dl, when the higher value must be 78 mg/dl).

The clinical signs entered in remission during the hospitalization, and the patient was discharged on the next day, medicated with citicoline 100mg/ml in a dose of 80 mg per kilogram (*Startonyl*®) whilst waiting for the neurological appointment.

6.5.2. Neurological appointment (11th April 2016) at RRV – Neurological examination

At the neurological examination, it was possible to observe vestibular ataxia characterized by head tilt to the right side, with difficulty to walk or stand, tending to lean or fall. The patient also showed exaggerated head movements, with bilateral large head oscillations. It presented rotational/horizontal nystagmus (with fast component to the left side, which did not alter with different head positions). Oculocephalic reflexes were inconsistent.

Despite of being severely disoriented, it was possible to perform the postural reactions, which were normal on the four limbs. It had not presented any other neurologic deficits.

6.5.3. MRI report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

The neurocranium appeared symmetrical, without any space occupying lesions or relevant sign alterations before and after paramagnetic contrast administration, suggesting neoplastic, inflammatory or vascular disease. The middle and inner ear had no significant alterations or lesions.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.5.4. Medical considerations/differential diagnosis

The clinical signs indicated a bilateral vestibular disease (predominantly to the right side).

The differential diagnoses include bilateral peripheral vestibular disorder, possibly as consequence of an idiopathic process (geriatric, on this case), toxic (e.g. metronidazole), metabolic (hypothyroidism, hyperadrenocorticism), paraneoplastic process, or vascular pathology (such as inner ear hypoperfusion or blood hyperviscosity); and a central vestibular syndrome, non-detectable on low field RM (microvascular disease, brainstem hypoperfusion or hypertension).

Is was recommended to discard the above described possible causes, and: symptomatic treatment was suggested (such as antiemetic or antivertiginous medication, like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day or metoclopramide 0.4mg/kg q6h, *per os*), as well as adequate physiotherapy (to help recovering from the vestibular ataxia) (Brum *et al*, 2010; Nelson & Couto, 2014; Plumb, 2011).

6.5.5. Disease progression

The patient was medicated with metoclopramide (0.4mg/kg q6h, *per os*), as suggested on the neurological appointment (Plumb, 2011).

It was performed a complete blood analysis (which revealed normal thyroid function), thorax radiography (without any evident lesions) and abdominal ultrasound (revealing only an increased echogenicity on the kidney cortex, compatible with non-pathologic aging process, interstitial nephritis, glomerulonephritis or nephrocalcinosis).

The results of the ancillary tests did not reveal any significant abnormality, and the clinical signs showed signs of improvement in a few days, with an almost complete remission after three to four weeks. This clinical manifestation is highly suggestive of bilateral idiopathic vestibular disease, despite being uncommon the bilateral exhibition of this syndrome (Nelson & Couto, 2014; LeCouteur, 2003; Thomas, 2000).

One year later, a splenic tumor was diagnosed, and the animal was euthanized a few months after the diagnosis.

6.6. CASE 6

6.6.1. Animal demographics and anamnesis

A male and non-neutered Cocker Spaniel dog with fourteen years old, weighting 12.1 kg, was referenced for neurological appointment at RRV in October 12th, 2011.

This dog had a history of a preputial mass, and heart murmur (grade II/III) without any clinical signs, and recurrent otitis. At October 8th, 2011 the patient started losing the strength on the hindlimbs, exhibiting head tilt to the left side, and emesis. It was hospitalized for five days in another veterinary facility, where it was performed a neurological examination and several ancillary diagnostic tests. In the first neurological examination, it was detected a non-ambulatory tetraparesis, rotatory nystagmus, vestibular ataxia (asymmetrical, to the left side), proprioceptive deficits (more evident on the left biped), and inconsistent menace response. There was no evidence of trauma.

The blood analysis (hemogram, liver, kidney and thyroid function, and ionogram) revealed a slight lymphopenia and hypomagnesaemia. It was medicated with Maropitant 2mg/kg, *per os*, once a day (*Cerenia* ®) and Sucralphate 1 g *per dog*, *per os*, twice a day. The thoracic radiography (latero-lateral projection), revealed an increased VHS[1] (11.3). The patient was medicated with Benazepril Chloridrate in a dose of 1mg/kg SID (*Fortekor*® 5mg) and Atenolol 0.52mg/kg BID.

6.6.2. Neurological appointment (12th October 2011) at RVV – Neurological examination

On the day of the neurological appointment, the animal was mildly depressed. The neurological examination revealed asymmetrical vestibular ataxia (tending to lean or fall to the left side), without postural reactions deficits. It also presented rotatory nystagmus (not changing with different head positions).

[1] VHS – Vertebral Heart Score is a mean to detect the presence and degree of cardiomegaly in dogs and cats, regarding the good correlation between body length and heart size. This measurement is obtained using a thoracic radiography of latero-lateral projection, the cardiac long axis is obtained measuring the length between the ventral border of the main bronchus and the most ventral aspect of the heart apex. This distance is compared with the thoracic spine, starting at the cranial edge of T4 vertebrae and is measured till the closest vertebrae. The normal values range between 8.5 and 10.5 (Nelson & Couto, 2014).

6.6.3. MRI report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

It was evaluated the neurocranium, including the respective peripheral vestibular components (inner/middle ear and vestibulocochlear and facial nerve) before and after the paramagnetic contrast administration. It had not revealed any significant alterations suggesting any neoplastic, inflammatory or vascular disease.

It was collected CF during the MRI procedure, which was normal and only revealed the presence of two cells per microliter.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.6.4. Medical Considerations/differential diagnosis

The clinical data and the MRI exam indicate a peripheral vestibular disorder, possibly of idiopathic origin. Other differential diagnosis may be suggested, such as metabolic causes (such as hypothyroidism, kidney, liver or electrolytic dysfunction, hypertension), paraneoplastic process or vascular lesions (micro infarctions or TIA, non-detectable on low field MRI equipment).

The frequent recurrent otitis may also be the cause of this disorder, despite of the absence of any evident lesion on the middle or inner ear, or in other peripheral vestibular structure.

Symptomatic treatment was suggested (such as antiemetic or antivertiginous medication, like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day or metoclopramide, 0.4mg/kg q6h, *per os*) (Brum *et al*, 2010; Nelson & Couto, 2014; Plumb, 2011).

6.6.5. Disease progression

Two days after being observed at RRV, the patient was already ambulatory, being able to go up and down stairs. It stopped the emesis and diarrhea episodes and was medicated with metoclopramide 0.4mg/kg q6h, *per os* (*Primperan*®) (Plumb 2011).

The patient was re-evaluated 10 days after and showed a significant remission of the clinical signs, but still with a slight residual head tilt and ataxia. It was also presenting bilateral external otitis (only presenting erythema, it was medicated for one week with *Otodine*®, an aqueous solution including Chlorhexidine Digluconate and Ethylenediaminetetraacetic acid).

About one year later, an echocardiogram was performed, revealing mitral insufficiency (without cardiac congestion). The patient was medicated with Benazepril Chloridrate in a dose of 1mg/kg SID (*Fortekor*® 5mg) and Atenolol 0.52mg/kg BID. Two years after the first neurologic signs emerge, the patient started exhibiting emesis, vestibular ataxia with tetraparesis, horizontal nystagmus, decreased menace response, right head tilt and slight multifocal pain. The blood analysis only detects a ALP increase (210 mg/dl, when the maximum range value is 160mg/dl). The X-ray examination to the thorax revealed a decrease of the L2-L3 intervertebral space, spondylopathy, and the presence of mineralized material on the L3-L4-L5 intervertebral spaces. Due to the persistency of the neurologic clinical signs, the animal was euthanized two days after. This second episode of neurologic signs was probably a recurrence of the peripheral vestibular disease.

6.7. CASE 7

6.7.1. Animal demographics and anamnesis

A non- spayed *Yorkshire Terrier* male dog, with four years old, weighting 3.7 kg, was referenced for neurological appointment at RRV at 1st, April 2016.

It had been recurrent episodes of vomiting and diarrhea for about one year before the neurological appointment. It was submitted to several treatments with gastroprotection drugs (active principles were not revealed).

One week before the clinical signs worsened, started having hematochezia and Hypothermia. The patient was interned on a veterinary clinic, where it was submitted to fluid therapy and calcium supplementation (due to a detected Hypocalcemia of 7.5mg/dl, when the minimum range is about 9.3 mg/dl).

Several exams were performed, including blood analysis and the ACTH stimulation test, which revealed that the animal was suffering from hypoadrenocorticism or *Addison*'s Disease. The patient was submitted to Dexamethasone IV therapy in a dose of 0.2mg/kg (in *S.O.S*), and hydrocortisone, as a constant CRI of 0.3 mg/kg/h IV on the following day (Plumb, 2011). The animal was after treated with Prednisolone 0.75mg (manipulated pills, one pill, twice a day).

Two days before the appointment it started presenting repetitive bilateral oscillations of the head, circling (both sides) and tending to fall. The animal had not light pupilar reflexes (on both eyes). Despite of being lethargic, it remained conscious, recognizing people and surrounding situations.

6.7.2. Neurological appointment (1st April 2016) at RRV – neurological examination

At the neurological examination the patient was slightly depressed and disoriented. It presented symmetric vestibular ataxia, including disequilibrium and frequent falls, lateral large oscillations of the head.

Evaluating the cranium, the oculocephalic reflexes were absent on both eyes, without any nystagmus or strabismus. Menace responses and light pupilar reflexes were present.

With an adequate support it was possible to perform relatively normal postural reactions.

6.7.3. MRI Report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

The neurocranium was symmetrical, without any space occupying lesions or evident sign alterations suggesting inflammatory, neoplastic or vascular disease. It was also evaluated the inner/middle ears, which didn't exhibit any significant alterations.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.7.4. Medical Considerations and Differential Diagnosis

These clinical signs were suggestive of a bilateral vestibular syndrome, apparently peripheral, attempting the neurological clinical signs and the imagological results.

Several differential diagnoses are suggested, such as Bilateral Vestibular Syndrome, Inflammatory disease (peripheral or central) "obliterated" by the recent corticosteroid therapy. The respective prognosis depends on the cause (spontaneous recovery is common on idiopathic vestibular disease).

Is was recommended to discard any additional causes (vascular, metabolic or paraneoplastic) and symptomatic treatment was suggested (such as antiemetic or antivertiginous medication, like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day or metoclopramide, 0.4mg/kg q6h, *per os*) (Brum *et al*, 2010; Nelson & Couto, 2014; Plumb, 2011).

6.7.5. Disease progression

It was performed several exams, including blood analysis, abdominal ultrasound, thoracic radiography and echocardiogram, which had not revealed any evident alteration.

The animal had exhibited a complete recovery within two to three weeks, despite of being treated with prednisolone during the recovery process (doses is described above).

6.8. CASE 8

6.8.1. Animal demographics and anamnesis

A spayed mixed breed queen, with seven years old, weighting 3.7 kg was referenced for neurological appointment at RRV at 14th, January 2016. Three days earlier, the patient started showing acute clinical neurological signs, without any evident trauma association. The animal was disoriented, presenting vestibular ataxia and lateral and/or vertical exacerbated head oscillations. There was no evidence of trauma.

6.8.2. Neurological appointment (14th January 2016) at RVV – neurological examination

The animal had vestibular ataxia, disorientation, vertical or lateral exaggerated head oscillations. By evaluating the neurocranium, it was possible to detect the absence of oculocephalic reflexes and menace response (both eyes), despite having normal pupilar reflexes. Due to the evident ataxia it was difficult to perform the postural reactions. The remaining neurological examination was normal.

6.8.3. MRI Report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

The neurocranium was symmetrical, without any space occupying lesions or evident sign alterations suggesting inflammatory, neoplastic or vascular disease. It was also evaluated the inner/middle ears, which didn’t exhibit any significant alterations.

The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

6.8.4. Medical Considerations and Differential Diagnosis

The neurological clinical signs were compatible with bilateral peripheral vestibular syndrome. The absence of any significant alterations on the MRI exam may suggest the presence of an idiopathic disease.

It was recommended to perform ancillary diagnostic exams to detect eventual causes, such as Viral diseases, hypertension or toxic, metabolic or paraneoplastic alterations,

resorting a cardiovascular evaluation (including SBP measuring), metabolic review and abdominal ultrasound or thoracic radiography.

Symptomatic treatment was suggested (such as antiemetic or antivertiginous medication, like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day or metoclopramide 0.4mg/kg q6h, *per os*) (Brum *et al*, 2010; Nelson & Couto, 2014; Plumb, 2011).

6.8.5. Disease progression

After two to three weeks after beginning treatment, during clinical re-evaluation, the animal had total remission of the clinical signs. Blood analysis parameters (including biochemical serum evaluation, biliary acids and clotting tests) were normal.

6.9. CASE 9

6.9.1. Animal demographics and anamnesis

A spayed mixed breed queen, with eighteen years old, weighting 3 kg, was referenced for neurological appointment at RRV at 9th, November 2015.

The patient was treated for fourteen days with Gentamicin, 2.2 mg/kg SC, once a day, after developing an urinary infection (Plumb, 2011). A few days before the appointment it started exhibiting disequilibrium that worsened, even after stopping the antibiotic therapy (at 3rd November). The animal was tending to fall and lean to the right side. There was no evidence of trauma.

Simultaneously this patient was presenting several clinical signs since 2014, whilst the cohabitant cat died. It was hyporexic since that period, having episodes of constipation, simultaneous *Haemobartonella* spp. infection (it was submitted to a double blood transfusion due to a severe anemia). On the following two months, it developed a mild kidney failure.

On the same year it started presenting Small intestine diarrhea and emesis and was diagnosed with Lymphoplasmocytic enteritis and pancreatic failure. The therapy consisted on alternating administration of Metilprednisolone, 2 mg *per os* divided into four times a day and Chlorambucil, 2mg *per os*, each 48 hours, due to the developed kidney failure. It also had started presenting frequent urinary infections.

The patient was treated with several drugs (including homeopathic drugs). Amlodipine, 0.625mg *per cat*, *per os*, once a day; Atenolol, 3mg/kg, *per os*, twice a day; Benazepril Chloridrate, 0.25mg/kg, *per os*, once a day (*Banacep*®); Chlorambucil 2 mg, *per os*, each 48 hours (*Leukeran*®); Famotidine, 1mg/kg, *per os*, once a day (*Lasa*®); Maropitant 2mg/kg, *per os*, once a day (*Cerenia*®); Prednisolone 0.8 mg/kg, *per os*, once a day (*Lepicortinolo*® 5 mg, half a pill, once a day) (Plumb, 2011); *Arsenicum*; Digestive enzymes (including protease, lipase and amylase – *Amyladol* ®); *Rheum officinale* extract, a food supplement for kidney failure (*Rubenal*®); Silybin (*Legaphyton*®); an homeopathic product used for urinary disease, including *Sabal Serratum*, *Berberis Vulgaris*, *Causticum Hahnemanni*, *Cantharis*, *Plumbum aceticum* and *Alumina* (*Reneel*®); a food supplement for nutritional support (*Redartik*®, composed by *Krill* oil, MSM, Jelly, Glycerin, soy oil , Zinc Metionate, Vitamin A, C and E, Biotin, L-Selenometionine, Colloidal silica)

6.9.2. Neurological appointment (9th November 2015) at RRV – neurological examination

The neurological examination revealed asymmetrical vestibular ataxia (right ataxia), with some signs of cerebellar alteration, namely postural hesitation, suggesting intention tremor. The remaining neurological evaluation was considered normal.

6.9.3. MRI Report

The T1W, T2W, STIR and FLAIR MRI sequences of the neurocranium were performed before the IV paramagnetic contrast administration (Gadolinium), and the T1W, FLAIR and 3D-T1W MRI sequences after its administration.

The neurocranium evaluation revealed a slightly atrophic encephalon (figure 8) (probably due to the advanced age of the animal), but without marked alterations on both neurocranium, middle/inner ear and vestibulocochlear nerve, suggesting inflammatory, vascular or neoplastic disease.

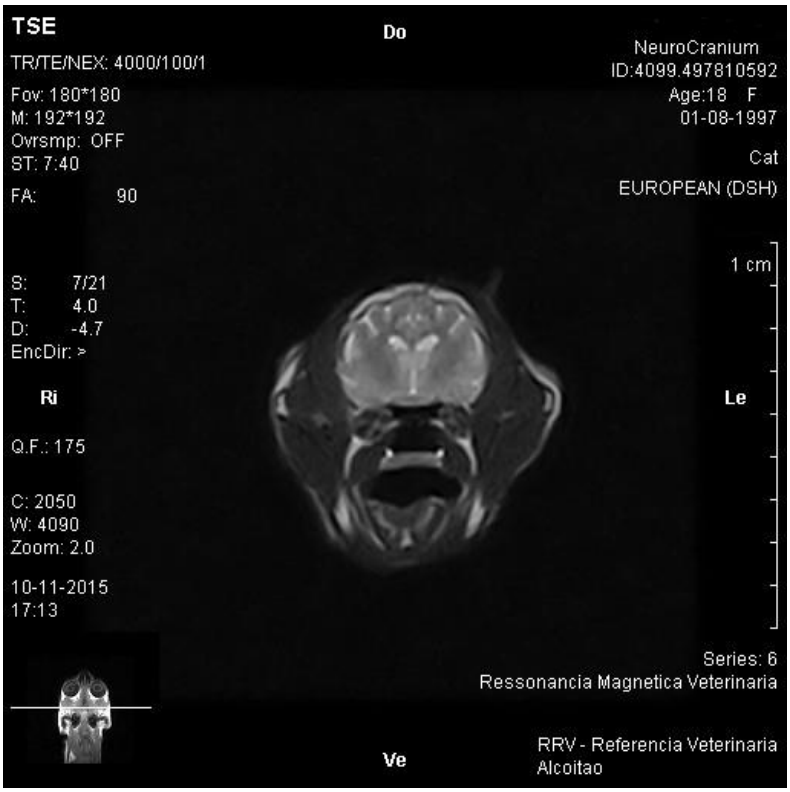

Figure 9 – T2W Sequence of the neurocranium revealing a slight encephalic atrophy.

6.9.4. Medical Considerations/ Differential Diagnosis

The neurological signs exhibited are not suggestive of any structural or morphologic encephalic lesion and probably is due to a toxic, metabolic or vascular alteration. Idiopathic disease is also probable, despite of the uncommon presentation (bilateral vestibular syndrome, accentuated to the right side) (LeCouteur, 2003; Thomas, 2000).

It was recommended to perform ancillary diagnostic exams to detect eventual causes, such as Viral diseases, hypertension or toxic, metabolic or paraneoplastic alterations, resorting a cardiovascular evaluation (including SBP measuring), metabolic review and abdominal ultrasound or thoracic radiography.

Symptomatic treatment was suggested (such as antiemetic or antivertiginous medication, like Betahistine Dihydrochloride 0.5mg/kg, *per os*, twice a day, Meclizine 25mg *per dog*, *per os*, once a day or 4mg/kg *per os*, once a day or metoclopramide 0.4mg/kg q6h, *per os*) (Brum *et al*, 2010; Nelson & Couto, 2014; Plumb, 2011).

6.9.5. Disease progression

Blood analysis were performed but had not revealed any evident alterations.

The clinical signs suddenly disappeared within a month (without any remaining signs). The animal was treated with Propentofylline (*Karsivan*®) and Cyanocobalamin, Pyridoxine Chloridrate and Tyamine Disulfide (*Neurobion*®) during the recovery.

The Veterinary professional assisting this patient before the neurological appointment referred that it was submitted to a mild anesthesia (Butorphanol, diazepam and Propofol, which doses were not revealed) to perform an oral cavity procedure, two weeks before the clinical signs onset

In July 2016, it was diagnosed a mammary carcinoma and the treatment consisted on conservative therapy (ending up dying in September 2016).

7. Discussion

The term "*Idiopathic*" is referred to characterize diseases without known causes (and not to characterize the absence of predisposing causes). The development of new and more sensitive imagological diagnostic methodologies may enable the discovery of eventual causes of vestibular disease, which are currently considered idiopathic.

Diagnosing an animal with Idiopathic Vestibular Syndrome is arduous once it requires the exclusion of several diseases. Besides that, some owners impose some limitation when accepting the performing of different ancillary diagnostic tests, usually due to economic constraints.

The currently available diagnostic equipment's (i.e. low field MRI equipment's) do not usually allow the detection of small vascular lesions, such as brain infarctions or TIA in dogs and cats that may lead to vestibular signs.

Besides that limitation, the blood collect for fibrine D-dimers determination may be useful to detect blood clotting alterations, but usually is not performed on the clinical signs onset and takes too much to be analyzed, thus it generally does not prove useful on vascular lesions detection or treatment (Nelson & Andreasen, 2003; Ettinger & Feldman, 2005). Despite of being very sensitive for vascular clotting alterations, it may be altered by other diseases, such as immune-mediated hemolytic anemia, liver or kidney lesion, neoplasia, congestive heart failure or following surgeries (Hillock *et al*, 2006).

However, nowadays it is increasingly common to diagnose Cerebral vascular accidents in dogs and cats.

Cats and dogs may exhibit different vestibular signs. Cats assume a wide-based stance and, despite of being possible to occur, is less common to occur nausea and vomiting in cats in the first stages of a vestibular disease with an acute onset (LeCouteur, 2003). Cats may have nystagmus with a certain direction earlier and develop contralateral nystagmus later (which is explained by the progression of an irritating lesion from ipsilateral to bilateral) (LeCouteur, 2003).

Regarding specifically the feline idiopathic disease, it may occur in cats of all ages, commonly on summer and early fall, with no gender or breed disposition. It is described the concurrent appearing of upper respiratory tract disease (which did not occur on the feline sample collected) (Nelson & Couto, 2014; LeCouteur, 2003). Some authors

describe that most of the cats suffering from idiopathic vestibular syndrome have outdoor access, which may be related with *Cuterebra* larvae myasis, not seen in Portugal (Glass *et al*, 1998; Lowrie, 2012b; Bagley, 1997).

Cats use to cry continuously, leaning against walls to additional support or maintain crouched and motionless (Negreiros, 2012).

A mild head tilt may persist, as well as, the reoccurrence of some of the clinical signs when the animal is blindfolded or exposed to darkness. The recovery may require two to four weeks (LeCouteur, 2003; Vernau & LeCouteur, 1999).

It is not common to occur concurrent facial paralysis and/or Horner's syndrome in patients on which idiopathic vestibular disease is suspected. Usually it is due to additional causes that may be fully investigated (Lowrie, 2012b).

Horner's syndrome may occur when some of the postganglionic Sympathetic axons following several cranial nerves are injured. It may happen in middle ear injuries, once they course through this structure (i.e. *Otitis Media*). This syndrome usually precedes facial paralysis signs (Lorenz *et al*, 2011; Schunk, 1988; Garosi *et al*, 2012).

Middle ear lesions may also lead to facial nerve paralysis since it exits the brainstem and courses by the facial canal, opening to the middle ear (Lorenz *et al*, 2011; Jeandel *et al*, 2016).

Although those are not commonly associated with idiopathic or peripheral vestibular disease, both oculosympatethic and facial nerve path are anatomically close to the petrosal portion of the temporal bone. The facial and vestibulocochlear nerve enter together in the petrosal bone, by the internal acoustic meatus. Thus, it is possible to coexist facial nerve paralysis and Horner's syndrome on vestibulocochlear nerve lesions (in which Idiopathic vestibular disease is included) (Garosi *et al*, 2012).

Both described paths course through the middle ear, but a lesion affecting only this structure may not lead to vestibular signs. It is required an extension of inner ear lesions to the middle ear (i.e. *Otitis interna* or inner ear inflammation spreading for the middle ear) (Chrisman, 1980).

Additional drug therapy may be used to compensate the vestibular signs. The most resorted drugs for vestibular disease are anticholinergics, antihistamines and

benzodiazepines (as well as antiemetic drugs to prevent or diminish any associated nausea or vomiting) (Thomas, 2000).

The anticholinergic drugs decrease the excitability of the neurons in the Vestibular nuclei, inhibiting the response to vestibular stimulation (Thomas, 2000).

The antihistamines (e.g. Meclizine, Dimenhydrinate) also have depressant properties on the vestibular system due to a residual anticholinergic effect. Phenothiazine drugs have both antihistaminic and anticholinergic activity, thus it administration is also reported (Thomas, 2000).

Benzodiazepines may help on the vestibular signs decreasing the resting activity of the vestibular nuclei neurons (Thomas, 2000).

These drugs act inhibiting the vestibular tone from the contralateral normal vestibular system, contributing to compensate the unbalanced vestibular input (Thomas, 2000).

Propentofylline is currently administered on dogs with cognitive dysfunction, but it may also be useful when vascular infarctions or TIA are suspected (or any vascular alteration leading to vestibular signs), since it improves the blood flow. It acts on blood dynamics suppressing platelet aggregation and thrombus formation, improving the erythrocytes flow and decreasing the peripheral vascular resistance (Landsberg *et al*, 2011).

Vitamin B complexes, including Cyanocobalamin (Vitamin B12), Pyridoxine (Vitamin B6) and Thiamine (Vitamin B1) may be administered as nutritional supplementation in animals suffering from vestibular disorders. It may act as nutritional support for neurologic activity since it may be involved on processes such as, tryptophan conversion to serotonin or niacin, GABA synthesis in the Central Nervous System or glycogen breakdown (Plumb, 2011).

Corticosteroid therapy is currently used in neurologic Veterinary Medicine. To address some disorders, such as immune-mediated diseases, corticosteroid-responsive meningitis, idiopathic meningoencephalomyelitis or even CNS neoplasia. The use of corticosteroid therapy may be beneficial once it is immunosuppressive, anti-inflammatory, reduces the tumors associated CNS edema and decreases the CSF production (Jeffery, 2014).

But, the corticosteroid therapy causes various controversial effects on neurologic recovery.

The immunosuppressive properties may also be prejudicial in some diseases, such as infectious diseases. Besides that, the synthetic corticosteroids have similar action of endogenous cortisol, which may predispose to infectious processes (Aharon *et al*, 2017). Also, corticosteroids may contribute to blood stasis and to a higher blood clotting rate, increasing the susceptibility to thromboembolism, brain infarctions or TIA (Aharon *et al*, 2017).

Corticosteroid administration is controversial on CNS trauma, including spinal cord injury, such as herniated discs, once it decreases the capacity of tissue regeneration and may accelerate de neuronal death after several CNS insults (Aharon *et al*, 2017; Jeffery, 2014). Additionally, the side effects of muscle loss and infection susceptibility support the contraindication of steroidal therapy on CNS trauma (Jeffery, 2014).

As previously described, the peripheral vestibular apparatus may be impaired by congenital, metabolic, neoplastic, inflammatory, infectious, iatrogenic/toxic, idiopathic or traumatic causes.

Most congenital vestibular diseases affecting the peripheral vestibular apparatus have no identified origin, despite of a hereditary basis being suspected. The exhibited signs seem to be originated from the impairment of both vestibular and auditory receptors (Chrisman, 1980).

Regarding the metabolic causes, hypothyroidism may result in vestibular disorders since it can lead to a myxomatous compression of cranial nerves whilst exiting the foramina due to myxedematous deposits accumulation, causing a neuropathy (Rossmeisl, 2010; Lowrie, 2012b). Decreased axonal transport and Schwann cells dysfunction are also reported anatomopathological mechanisms (Kent *et al*, 2010). Dogs with hypothyroidism may also present generalized weakness, lethargy and/or unilateral or bilateral facial paralysis (Rossmeisl, 2010; Lowrie, 2012b; Thomas, 2000).

Some dogs with hypothyroidism presenting vestibular signs may have abnormal brainstem auditory evoked responses, as well as altered electromyographic results on the appendicular muscles (Scott-Moncrieff, 2007).

Commonly, inflammation of the medial ear may extend to the inner ear and lead to vestibular signs (e.g. Otitis media/interna or neuritis of the vestibulocochlear nerve). In cats it is common to occur inflammatory nasopharyngeal polyps through the tympanic

cavity and auditory apparatus, leading to vestibulocochlear nerve compression (due to tissue swelling) and neuropathy (Chrisman, 1980; Thomas, 2000; Rossmeisl, 2010; Schunk, 1988).

Infectious origins commonly reside on otitis media extending to the inner ear (leading to otitis interna), but it also may occur due to pharynx infections spreading via the auditory tube, mostly originated from bacterial infection (such as *Staphylococcus* spp., *Streptococcus* spp. or *Escherichia Coli*), but yeast, parasitic or foreign bodies origins are also possible (Schunk, 1988). Otitis media/interna usually occurs after Otitis externa, thus it is essential to perform a basic otologic examination to detect any alterations, such as cerumen presence (Kent *et al*, 2010).

The vestibular signs appearing after otitis media/interna are secondary to the several alterations that occur on the auditory apparatus and that may be observed by radiography and CT scan, including the presence of fluid or tissue within the tympanic bulla and it thickening or lysis, osseous proliferation of the petrosal bone (Kent *et al*, 2010). Those alterations may lead to neuritis of the vestibulocochlear nerve after compromising the membranous labyrinth (Schunk, 1988).

Trauma involving the base of the skull, tympanic bulla or petrosal bone may also prompt vestibular signs once it may compromise the vestibular apparatus. Thus, it is important to perform radiographic examination of the tympanic bulla, when trauma and fracture are suspected (Chrisman, 1980).

Ototoxicity may occur after parenteral administration of aminoglycoside antibiotics or other drugs like furosemide or chemotherapy compounds or antiseptic agents, such as Chlorohexidine. These compounds may lead to both vestibular and auditory degeneration (Chrisman, 1980).

The aminoglycoside antibiotics concentrate mostly in the endolymph and perilymph, damaging the hair cells (Kent *et al*, 2010).

Frequent ear flushing may lead to vestibular impairment after mechanical insult or aggressive irrigation. Additionally, it may translocate bacteria or bacterial products through the medial ear and then penetrate the vestibular window, reaching the inner ear (Kent *et al*, 2010).

Paraneoplastic syndrome is rarely documented in veterinary medicine but it may lead to various neuropathies, usually involving all the limbs (tetraparesis) (Cuddon, 2002). Paraneoplastic neuropathy due to lymphosarcoma may exhibit multifocal mononeuropathies involving cranial nerves and peripheral nerves, usually the trigeminal and facial nerves (Cuddon, 2002).

Continuous systemic hypertension may result in hypertensive encephalopathy in both dogs and cats (Kent, 2009; Jepson, 2011). This condition is associated with several lesions, such as hyperplastic arteriosclerosis of cerebral vessels, interstitial white matter edema and parenchymal microhemorrhages (Jepson, 2011).

Both persistent hypertension and hypothyroidism may lead to spontaneous thrombosis, infarction and hemorrhage and vestibular signs may be exhibited. Other vascular alterations, such as thrombocytopenia and clotting disorders may also urge spontaneous hemorrhage (Bagley, 1997).

The ancillary diagnostic tests also may fail to detect some lesions due to the absence of sensitivity. The thoracic radiography is an important mean to detect the presence of metastatic pulmonary lesions, but it only allows to detect lesions with 7mm of diameter or larger (comparing with CT scan that may detect lesions at least with 1mm of diameter) (Nemanic *et al*, 2006).

On MRI is important to resort the administration of paramagnetic contrast media, usually Gadolinium based agents. The paramagnetic contrast agents may increase the difference on signal intensity between different tissues, based on the different Protons response to Radio-frequency pulses towards a strong magnetic field (Kuriashkin & Losonsky, 2000).

The image contrast may be improved or modified by increasing or decreasing the signal intensity between different tissues. When administered intravenously it is usually targeted to CNS lesions, allowing a better definition of the margins of each lesion as well as achieving an accurate differentiation of the lesions (Kuriashkin & Losonsky, 2000).

The etiology of the idiopathic vestibular disease remains unknown, but some probable causes are proposed, such as abnormal production, circulation and absorption of the endolymphatic fluid and neuritis of the vestibular portion of vestibulocochlear nerve (Schunk, 1988).

Additionally, some mild structural alterations are proposed, such as early Otitis media/interna, non-detectable on low field MRI or CT scan (which requires treatment and does not resolve spontaneously) (Negrin *et al*, 2010; LeCouteur, 2003).

On the USA, the seasonal occurrence of feline vestibular idiopathic on outdoor cats may be related with *Cuterebra* larvae aberrant migration through the inner ear, but such cause is not reported in Portugal (Vernau & LeCouteur, 1999).

Similarly to the human vestibular neuritis due to herpesvirus-1 infection, it is also reported in dogs a canine herpesvirus-1 infection of the vestibular labyrinth and ganglion that may lead to vestibular signs (Parzefall *et al*, 2011; Thomas, 2000).

In general, the described clinical cases evolved according to the literature. All the described cases had an acute onset of the clinical signs, which had a continuous regressive pattern into the total remission without medication, except for the case 4 (presenting frequent and intermittent episodes, suggestive of a vascular etiology). Recurrence was only described in one case (case 6), and case 1 presented central vestibular signs a few months after the initial vestibular signs. Except for case 7, all the dogs were senior when presenting the first clinical signs.

During the investigation of each clinical case no other cause for the vestibular signs was found; only in case 1 was diagnosed primary hypothyroidism, possible etiology for the vestibular signs. Case 2 presented inactivity of the Cochlear portion of the Vestibulocochlear nerve when submitted to the BAER test.

Case 4 presented mineralization of the auditive conducts (bilaterally) on the CT scan, common in geriatric animals which suffered from chronic otitis, without any clinical signs. The MRI did not exhibit any abnormal intracranial alterations, including tympanic bulla, inner ear, vestibulocochlear and facial nerve lesions.

Case 9 was treated with gentamicin via SC for fourteen days after developing UTI and the recommended treatment period for Urinary infections is less than seven days. Since gentamicin is an aminoglycoside, the exhibited vestibular signs might be a consequence of ototoxicity (iatrogenic origin) (Plumb, 2011).

None of the cats included on the sample had presented upper respiratory tract disease before the vestibular signs onset.

8. Conclusions

Diagnosing IVS is arduous, it is important to invest on a complete neurological examination and several ancillary diagnostic tests to exclude the presence of other causes.

The limited capacity of diagnostic equipment, such as MRI or Radiography equipment, may hide the presence of micro lesions originating vestibular signs. The economic restriction of the owners may also limit a complete investigation.

IVS is commonly misdiagnosed with brain infarctions or TIA's and the fact of being associated with severe clinical signs with acute onset, may influence the decision of the euthanasia, limiting a further investigation.

Both facial paralysis and Horner's syndrome are possible to coexist with vestibulocochlear lesions, despite of not being associate with lesions of the vestibular apparatus.

There is no effective treatment for IVS and it is only recommended symptomatic medication to compensate the vestibular signs, such as antiemetic or anticholinergic therapy. Corticosteroid therapy has no beneficial effects on IVS progression.

The prognosis is good to excellent and, generally, the clinical signs enter in remission in three to four weeks in both cats and dogs, without any instituted medication. The recurrence of the clinical signs is rare.

Many causes for IVS are proposed, including occult OIM, abnormal production, circulation and absorption of the endolymphatic fluid, neuritis of the vestibular portion of the vestibulocochlear nerve, *Cuterebra* larvae aberrant migration (not present in Portugal) and herpesvirus-1 infection of vestibular labyrinth and ganglion in dogs.

Further work may be developed to access a better diagnostic of IVS, such as improving the MRI equipment's sensitivity or developing a *standard* diagnostic protocol to apply on cases which IVS is suspected.

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