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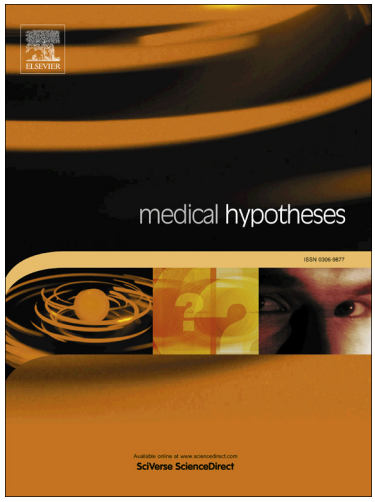

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A New Theory on GABA and Calcitonin Gene-Related Peptide Involvement in MdDS Predisposition Factors and Pathophysiology

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Abstract

Introduction: Mal de Debarquement Syndrome (MdDS) is a condition characterized by a sensation of motion in the absence of a stimulus, which presents with two onset types: Motion Triggered, and Spontaneous or Non-Motion Triggered MdDS. MdDS predominantly affects women around 40-50 years of age. A high number of MdDS patients report associated disorders, such as migraine and depression. The pathophysiology of MdDS is still unclear, and it remains obscure what predisposing factors might make patients more vulnerable to developing the condition. Hormonal changes as well as depression in women have been examined as potential key factors for developing MdDS. Studies on migraine and depression have revealed correlations with hormonal fluctuations in females as well as aberrant levels of some key neurotransmitters such as Gamma-Aminobutyric Acid (GABA) and inflammatory neuropeptides like Calcitonin Gene-Related Peptide (CGRP). Consequently, this manuscript aims to propose a new hypothesis on the predisposing factors for MdDS and a new concept that could contribute to the understanding of its pathophysiology.

New Hypothesis: Recent findings have demonstrated a role for hormonal influences in MdDS patients, similar to previous observations in patients with depression and migraine. We hypothesize an involvement of gonadal hormones and aberrant levels of neurotransmitters, including the GABAergic and serotonergic systems, in MdDS pathophysiology. Our theory is that certain patients are more vulnerable to develop MdDS during specific gonadal hormonal phases. Furthermore, we hypothesize that it may be possible to identify these patients by measurement of an existing imbalance in these neurotransmitters or inflammatory neuropeptides like CGRP.

Further Evaluation of the Hypothesis: According to one theory, MdDS is considered as a maladaptation of the Vestibular Ocular Reflex (VOR) and velocity storage. When considering this theory, it is essential to highlight that the brainstem nuclei involved in the VOR and the velocity storage include $GABA_b$ sensitive neurons, which appear to produce inhibitory control of velocity storage. Responses of these $GABA_b$ sensitive neurons are also modulated by CGRP. Thus an alteration of the GABAergic network by imbalances of inhibitory neurotransmitters or CGRP could influence signal integration in the velocity storage system and therefore be directly involved in MdDS pathophysiology.

Consequence of the Hypothesis and Future Studies: A predisposing hormonal and neurotransmitter imbalance may play a role in developing MdDS. Future studies should focus on the hormonal influences on neurotransmitters (e.g. GABA) and on the trial of CGRP antagonist drugs for MdDS patients.

Key words: Mal de Debarquement Syndrome – Gonadal Hormones – Migraine – Depression - GABA - Calcitonin gene-related peptide

1.Introduction

Mal de Debarquement Syndrome (MdDS), which is French for "sickness from disembarkation", is considered a neurological disorder. MdDS is characterized by a persistent sensation of self-motion, described as a sense of rocking, swaying or bobbing [1], which in most cases can lead to postural instability [2]. When disembarking from a vehicle, people often describe temporary sensations of unsteadiness and difficulty readjusting to a stable environment [3], a frequent phenomenon termed 'Mal de Debarquement' (MdD). In most cases these symptoms resolve within days and are non-pathological. On the contrary, when symptoms persist for months or years on end, symptoms become pathological and people are diagnosed with 'Mal de Debarquement Syndrome' [3]. In addition to self-motion sensations, MdDS patients also report secondary associated conditions and symptoms such as: migraine, depression, anxiety, unsteadiness, brain fog, cognitive difficulties, visual sensitivity and otological symptoms such as tinnitus and/or fullness of the ears [3–5]. Some MdDS patients describe that their symptoms fluctuate throughout the day and throughout the month [6]. A recent study found that a monthly aggravation of symptoms could be correlated to different hormonal phases of the menstrual cycle [7].

MdDS is a debilitating condition, known for having a high level of illness intrusiveness and a strong impact on a patient's quality of life [8], as well as imposing an economic burden on the patients and the healthcare system [9]. Currently, MdDS is considered an uncommon disorder [10], however, the definite prevalence of the condition is still unclear due to a lack of awareness amongst healthcare professionals [11, 12], though MdDS is estimated to affect 1.3% of patients that visit neuro-otology clinics [10]. Moreover, two main subtypes have been identified depending on the onset, but other features to justify the classification of these subtypes are still unclear. Typically, MdDS can be triggered by disembarking from a moving vehicle (e.g. after a cruise, flight, car ride, etc.) [13]; this is defined as Motion-Triggered (MT) MdDS. However, the same symptoms can also appear spontaneously, in which they are referred to as Spontaneous (SO) MdDS [11] or Non-Motion Triggered (non-MT) MdDS [2]. MdDS has also an unexplained distinct female predominance (9:1 female to male ratio), which has been widely described in several reports [3, 5, 10, 14–19]. Furthermore, the average age of onset is reported between 40 to 50 years of age [15]. Despite the fact that MdDS awareness and investigations have been growing over the past years, the knowledge of this

condition among health care professionals is still limited, resulting in a high number of misdiagnosed patients [11], as well as limited treatment options.

With regards to the underlying pathophysiology of MdDS, a few theories have been formulated; however, they remain partially invalidated. One theory, proposed by Dai and colleagues [1, 13], defines MdDS as the result of maladaptive coupling of multiplanar information of the Vestibular-Ocular Reflex (VOR), or to be put more simply, maladaptation of the VOR and the velocity storage mechanism. The VOR is the key reflex responsible for maintaining stable gaze during head rotation [2], ensuring that the image is stabilized on the retina [20]. The velocity storage mechanism is defined as a multisensory element comprising of central pathways that are responsible for extending vestibular inputs and retaining vestibular information. Velocity storage enables the adjustment of postural stability in specific contexts [21]. The VOR is able to adapt depending on the context, and it can have a gradual and long lasting "contextual" VOR adaptation [22, 23]. When a person is adapted to a specific context, for example in regards to MdDS we can talk of cross-axis adaptation present on a cruise ship. In other words, if an individual is rocking from side-side (roll) for example during passive motion on a cruise ship, and also rotating the head, for long periods of time, one might develop an inappropriate cross-coupling between roll and rotation, the so called cross-axis adaptation [1, 23, 24]. A similar cross-axis re-adaptation typically occurs when returning to a static environment. This re-adaptation mechanism, specifically after disembarking, might fail in MdDS patients, which could underlie their symptoms as postulated by Dai and colleagues [1].

Another theory that has been proposed, based on neuroimaging and neuromodulation studies in MdDS patients [16, 25], is that MdDS is a disorder of abnormal functional connectivity, driven by a central neural oscillator that becomes entrained during periodic motion exposure [6, 25–28]. This theory, by Cha and colleagues, was proposed after resting-state functional Magnetic Resonance Imaging (rsfMRI) studies showed increased functional connectivity between the left entorhinal cortex (EC) and amygdala, and visual and vestibular processing areas, as the result of decreased connectivity in multiple prefrontal areas [27]. In another study using 18F-fludeoxyglucose positron-emission tomography (FDG-PET), MdDS patients were observed to have hypermetabolism in the left EC and amygdala, compared to controls [10]. The EC area is

known to play a key role in mapping one's spatial environment [29] and the amygdala, which together with the hypothalamus, serves to reorient attention to functionally relevant internal and external stimuli [27]. Thus, according to this theory, the EC area has been suggested to be a key area in the pathophysiology of MdDS [10]. Additionally, a key area in cognitive control over spatial information processing and spatial working memory, the dorsolateral prefrontal cortex (DLPFC), has been shown to decrease in grey matter volume in MdDS patients, suggesting that both cognitive and emotional networks are affected in MdDS [16]. More research through voxel base morphometry analysis has shown that MdDS patients exhibit alterations in the grey matter volume in the visual-vestibular processing areas, a crucial area for perception of visual motion, and in the middle temporal area, which is considered as a vital centre for visual motion processing [25, 30].

These two primary theories regarding MdDS pathophysiology - the maladaptive VOR and neuroplasticity disorder - may not be mutually exclusive [6]. However, to date it remains unclear how they may be interrelated. In addition to these two major theories, an additional hypothesis to consider is that MdDS symptoms are generated as a pseudo-hallucinations from vestibular memory [15]. However, this theory has not been further investigated or adequately discussed. Many questions remain to be addressed considering MdDS pathophysiology. Ultimately, one of the main aspects to consider is the presence of predisposing factors. To date, it remains obscure why, for example, MT patients develop MdDS in a specific motion experience in their lifetime, despite having been most likely exposed to passive motion before, such as being on a cruise or in a car. Furthermore, the two main theories about MdDS do not fully explain the fluctuations of symptoms often reported by MdDS patients [31]. Thus, we intend to propose a new hypothesis about the underlying mechanism involved in MdDS pathophysiology. Our hypothesis takes into consideration the different types of onset of MdDS, elucidates potential predisposing factors, and accounts for fluctuations in symptom severity by taking into account observations from similar disorders that are often coexist in MdDS patients such as migraine and depression. If supported by existing and future investigations, this new hypothesis could increase the current understanding of MdDS and lead to new therapeutic options.

1.1 Hormones a predisposing factor to consider

When examining MdDS, it is essential to consider the clear female majority characterising this disorder [6, 11]. MdDS affects significantly more women and men, a situation similar to what is observed in migraine and depression. Despite this observation, the potential influence of female gonadal hormones on MdDS has only been recently examined through a retrospective questionnaire involving 370 MdDS patients [7]. In that study, the gender disparity (perhaps representing a hormonal component) was examined in order to assess if gonadal hormones were involved in onset, symptom fluctuation and therefore the underlying pathophysiology of MdDS.

From the results, reproductively active female patients with MT onset reported an aggravation of MdDS symptoms during different menstrual phases, similar to what is often described for patients with migraine [32] and in some cases for patients affected by depression [33]. This suggests that MdDS symptoms are influenced by hormonal changes. It is commonly known that females experience hormonal changes throughout their menstrual cycle, reporting mood and behavioural changes in parallel with the fluctuation of hormones, such as changes in progesterone, estrogen and luteinizing hormone [34]. Hormonal fluctuations have been found to play an important role in other vestibular disorders, such as vestibular migraine and Ménière's Disease [35] and more generally, female hormones are known to be related to migraine [32] and depression [36]. Moreover, in the same study it was also reported that MT female patients often recalled that they were menstruating during the time of the onset of MdDS symptoms [7], and it emerged that a higher number of SO patients reported suffering from irregular menses and migraine [7]. Despite the fact that these conclusions were based on retrospective data, which could be susceptible to recall biases, these hormonal observations suggest that particular hormonal phases may be predisposing factors for developing MdDS. When considering the hormonal phases in MdDS subjects, it has been also noted that female MdDS patients belong to a relatively narrow age group (onset is often between 40 to 50 years of age), which is in line with perimenopausal [2] and menopausal phases in women [6, 19]. From these preliminary results, it is possible to hypothesize that particular hormonal phases (perimenopause or menses) could act as predisposing factors rendering certain individuals more prone to develop MdDS.

Despite the small number of male patients affected by MdDS, the hormonal profiles and conditions of male

MdDS patients has been also recently assessed. From these preliminary findings, some male MdDS patients reported to have been using hormonal medications (particularly gonadal steroids), and some had been diagnosed with hypogonadism [7]. This also suggests that in male patients, hormonal changes and aberrations may influence the onset and fluctuations of MdDS symptoms.

1.2**Migraine and MdDS**

Another aspect to consider in relation to MdDS is migraine. MdDS has a strong interrelation with migraine, with a high number of MdDS patients reporting migraineous symptoms [10, 37]. Estrogen and other gonadal hormones have been implicated in migraine symptom fluctuation and pathophysiology [30,31]. In patients with migraine, the drop in estrogen (estrogen withdrawal) that is observed during menses, has been described as the principal cause for migraine vulnerability in females [32]. Female patients with migraine also experience symptom variability in response to fluctuating hormonal levels typical of pregnancy, menopause, Hormone Replacement Therapy (HRT) and the use of hormonal contraceptives [39–41]. Considering hormonal changes throughout different ages, along with migraine, headache and dizziness are also common symptoms of perimenopause [42]. In addition to the gonadal hormonal changes, it has been hypothesized that neurotransmitter changes related to different hormonal stages may also be responsible and involved in the pathophysiology of migraine [43]. For example, anomalies of the metabolism or of the release of Gamma-Aminobutyric Acid (GABA) and/or glutamic acid has been theorized before to be a predisposing factor influencing the occurrence and the frequency of migraine attacks [44]. GABA is the main inhibitory neurotransmitter, and it has several different receptors in multiple brain regions ($GABA_a$, $GABA_b$, $GABA_c$ [45]) [32, 46]. However, GABA is just one of the many neurotransmitters that may be relevant for migraine. In one of the several hypotheses for migraine pathophysiology, it has been proposed that estrogen may interfere with cellular excitability or cerebral vessels [32]. Estrogen and progesterone can influence pain-processing networks and the endothelium involved in the pathophysiology of migraine, and interrelationships between estrogens and brain neurotransmitters have been reported, including serotonin, norepinephrine, dopamine, and endorphins [32]. Considering the neurochemical changes, recent findings from animal studies have noted the implication of a neuropeptide named CGRP. CGRP is a 37-amino acid neuropeptide, that is widely distributed throughout the central and peripheral nervous systems [47] and is

involved in different biological processes such as neuromodulation, cardiovascular regulation, inflammation, metabolic function, and aging [48]. From recent findings, CGRP has been implicated in the pathophysiology of migraine, mainly after observing that CGRP levels were higher during a migraine attack [49]. Additional studies have demonstrated that CGRP can be influenced by hormonal changes [48]. CGRP is known to be involved in the "hot flashes" that typically occur during perimenopause and menopause [50] by acting centrally on the thermoregulatory areas of the hypothalamus as well as peripherally to cause vasodilation and sweating [51]. Similarly CGRP is also known to influence the trigeminal nociceptive system [49], possibly involved in migraine. Thus, from these recent findings new therapeutic options are emerging from the development of antagonistic CGRP drugs [47] to help manage migraine. The latest research is focusing on anti-CGRP monoclonal antibodies, as several antagonist of the CGRP receptor such as olcegepant, telcagepant led to the development of hepatotoxicity [47]. Monoclonal antibodies are large molecules that cross the blood-brain barrier in a small ratio of 1:1000; however, the latest research reported that these agents can be effective prophylactics. These results are promising, but the place of these expensive agents among the many demonstrated prophylactics for migraine is still not clear [47]. However, considering the strong link between migraine and MdDS [15], it is possible that this new therapeutic strategy of using antagonists to CGRP may hold some relevance with regards to treatment or prevention of MdDS.

1.3**Depression and MdDS**

Depression is another disorder that could influence MdDS patients (e.g., by making them more vulnerable), and that, similar to migraine is influenced by hormones and aberrant neurotransmitter levels. Depression is known to be more common in women [36], similar to what is described for migraine and MdDS. The relation between hormones and depression has been shown frequently [36, 52]. In fact, females report episodes of depression during periods of hormonal perturbation, such as: prior to menses, immediately after pregnancy, as well as during and shortly after menopause [36]. One of the major neurotransmitters attributed to depression is serotonin, and it is widely known that estrogen and progesterone are able to modulate different aspects of serotonergic function, demonstrating that gonadal hormones can influence the pathophysiology of depression and its treatment [36]. However, in addition to hormonal changes several

other neurotransmitters have been similarly considered when examining depression, such as dopamine, norepinephrine and the GABAergic system. For example, alterations of the GABAergic system are known to be interrelated in the pathophysiology of depression [53] and many studies have shown that the normalization of cerebral GABA deficits is associated with positive treatment outcomes [53].

Moreover, several studies have examined the role of CGRP in depressed patients [51, 54]. Increased levels of CGRP have been observed in depressed patients; however, these increases may be an adaptive response to the condition [54]. CGRP injections have been found to decrease depression-like behaviours [54], supporting the theory that elevated CGRP in depressed individuals may be an adaptive response to the disorder.

MdDS patients are likely to be affected by depression [8, 15], which could be due to a myriad factors including the constant strain of self-motion sensations, the lack of effective treatments, the significant lifestyle changes, etc. However, a recent study reported that MdDS patients from both onset types had a high percentage of pre-existing mood and anxiety disorders (prior to developing MdDS), suggesting that depression may not simply be a secondary mood disorder starting after MdDS onset. These findings suggest that mood disorders may have been premorbid risk factors [12]. Within this context, CGRP may also influence depression in MdDS subjects.

Considering the female predominance and the high risk of migraine and depression in MdDS patients, it is possible to formulate a new theory that includes hormonal changes, GABAergic system alterations and CGRP for MdDS pathophysiology.

2.**New Hypothesis**

Given the evidence that MdDS is more prevalent in female patients, that hormonal changes influence symptomatology and that patients are often affected by migraine and depression [4, 7, 12], we hypothesize that MdDS patients may suffer from a neurochemical imbalance during a particular hormonal phase, rendering them more susceptible to developing the condition when the onset of their MdDS occurs.

However, among the several neurotrasmitters that could be implicated in MdDS pathophysiology, GABA and the GABAergic system are most likely implicated. More specifically, we theorize that patients develop MdDS due to a pre-existing GABA and CGRP imbalance, which makes them more vulnerable to developing the condition. For this theory the MT onset is primarily considered.

3.**Hypothesis Evaluation – GABA involvement in MdDS pathophysiology**

Several neurotransmitters may be involved in MdDS pathophysiology; however, this manuscript and first hypothesis focuses mainly on GABA. We do not exclude the possibility that other neurotransmitters may be involved and responsible for MdDS.

In this section, the reasoning for the hypothesis is provided.

3.1**GABA and the VOR maladaptation theory**

If considering MdDS as a maladaptation of the VOR and velocity storage, it is essential to highlight that the brainstem nuclei involved within the VOR and the velocity storage are $GABA_b$ sensitive neurons. They are located in the medial and superior vestibular nuclei [55], which appear to produce inhibitory control of velocity storage. $GABA_b$ receptors are also widely distributed in the central nervous system, including the spinal cord and the granule cell layer of the cerebellum [56]. $GABA_b$ receptors enable GABA to produce a variety of effects on neuronal function. These receptors are located both pre- and post- synaptically, where they can be activated by synaptically-released GABA. The ability of $GABA_b$ receptors to regulate GABA release provides an important mechanism for the feedback control of both $GABA_a$ and $GABA_b$ inhibition. Thus, by acting at both pre- and postsynaptic sites, $GABA_b$ receptors have the potential to produce profound changes in neuronal function. Generally, GABA is the major inhibitory neurotransmitter in the cortex, activating both ionotropic and metabotropic receptors [57, 58]. $GABA_b$ receptors ($GABA_b$-Rs) are G-protein coupled receptors that modulate neuronal excitability [59, 60]. The involvement of $GABA_b$ receptors with the velocity storage is supported by studies where an intramuscular injection of a $GABA_b$ agonist, Baclofen, lead to a dosage-dependent suppression of the velocity storage [56]. Baclofen is known to act presynaptically as a selective inhibitor of the release of excitatory amino acids, in addition to this, it is

known for acting specifically on the $GABA_b$ receptors and to produce a post-synaptic inhibition in the hippocampus [56] and to affect the vestibulo-oculomotor system. Baclofen also has the ability to block alternating nystagmus induced in monkeys by surgical lesions [56]. As a result, Baclofen was previously used to confirm the ability to suppress or shorten the time constant of the velocity-storage mechanism [61] and that $GABA_b$ neurons were controlling the velocity storage.

When considering the high number of female patients who suffer from MdDS, and the reported fluctuations of symptoms in response to hormonal changes, it can be theorized that the $GABA_b$ sensitive neurons could be subjected to the GABAergic system changes that are induced by hormones [1]. From previous studies, it is known that low GABA plasma levels are associated with depression [62], something commonly reported in MdDS patients [3]. Similarly, when considering female hormones, low GABA plasma levels are characteristic in Pre-Menstrual Syndrome (PMS) sufferers in the luteal phase [46], which could suggest a period of symptom aggravation for female MdDS patients around menses. In addition, GABA-mediated neurons are known to have a prominent inhibitory role in spatial navigation. Consequently, their deregulation, by altering hormonal levels, could hold some significance in the aggravation and potentially in the development of MdDS symptoms [63].

3.2 **GABA and Female Hormonal Phases in developing MdDS:**

When considering MdDS subjects, a peculiar aspect to note is the patient's hormonal status during onset. As reported in a recent study [7], a large number of patients with MT onset reported to have been menstruating during the onset event. Our hypothesis proposes that low levels of plasma estrogen and GABA during this time may be predisposing factors for the development of the MT form of MdDS. Numerous studies have measured changes in GABA- related inhibitory function during different phases of a woman's reproductive life, i.e. during menses [46], pregnancy [64] and menopause [53], using methods such as *in vivo* proton magnetic resonance spectroscopy (^{1}H-MRS), transcranial magnetic stimulation, and cerebrospinal fluid analysis [53]. Those changes are the result of an acutely altered GABAergic system observed in different hormonal phases. Thus, with regards to MdDS, we hypothesize that a woman with a MT onset of MdDS during menses would have been predisposed to this condition by low estrogen and GABA plasma levels.

Fluctuations in gonadal hormone levels, which occur during menopause and perimenopause, have been reported to affect the GABAergic system [65]. This could explain why patients in this particular hormonal phase (e.g. perimenopausal) seem to be more predisposed to developing MdDS, as previously suggested by Hain in 1999 [19]. At this stage, it is impossible to determine whether such particular low plasma levels of GABA were present before MT MdDS patients developed MdDS. However, if GABA plasma levels could be assessed in these patients one could argue that aberrant GABA concentrations may have developed following onset. Thus, one way to further demonstrate if GABA plasma levels can be modulated and interfere with MdDS symptoms may be to have a follow-up of MdDS patients after remission of symptoms. For example, MT MdDS patients could be monitored after they have been successfully treated using the optokinetic treatment [2], for example, which is currently considered one of the most successful treatments for MT MdDS patients [66]. If the patients' GABA levels would change after remission then it would indicate that a potential aberrant GABA level may be a consequence of MdDS, while on the other hand, if patients regardless of their remission of symptoms report aberrant GABA levels, this could indicate a further characterization and perhaps predisposing factor of MdDS subjects.

3.3 **Effective Drugs for MdDS act on the GABAergic system:**

Another finding that supports our hypothesis that GABA may be implicated in MdDS pathophysiology is the positive effect of certain drugs in reducing MdDS symptoms, such as clonazepam, which acts on the release of GABA [5]. Similarly, from clinical observations it is known that diazepam and lorazepam are often used for other balance disorders [67]. An explanation could be that these drugs have a potential pathway for cortical modulation of noradrenergic effects, with the ability to act on spatial motion discomfort, anxiety, height phobia and the ability to lower anxiety [67].

In addition to this, it has been reported that gabapentin [15], a drug commonly used for epilepsy and also migraine [68] has a strong influence on GABA and glutamate levels, which could explain why MdDS patients benefit from the use of this drug. Similarly, amitriptyline, a tricyclic antidepressant that inhibits norepinephrine and serotonin uptake [69], has positive effects on MdDS patients, and is also prescribed to

migrainous patients [69]. One hypothesis for their action mechanism could be explained by their ability to block sodium-channels and enhance GABA-mediated inhibition [69].

3.4 GABA and MdDS as a neuroplasticity disorder:

When considering MdDS as a neuroplasticity disorder [10], it could be hypothesized that the hormonal receptors activated by gonadal hormones may also affect the hippocampal and EC interneurons. However, to date, estrogen receptors have not been specifically found in the EC area. Hormonal changes such as changes in estrogen levels are known to influence the GABA turnover in animal studies [70]. Similarly, as presented for the VOR maladaptation theory, GABA-mediated neurons are hypothesized to have a prominent inhibitory role in spatial navigation [63]. For example, the raphe-vestibular network is known to have to serotonergic and non-serotonergic neurons. The non-serotonergic neurons utilize a variety of transmitters. For example, 5-HT-negative cells in the dorsal raphe nucleus (DRN) include populations that express GABA, dopamine and neuropeptides [67]. The DRN sends serotonergic and non-serotonergic projections to the vestibular nuclei as well as in the amydgala [67], a region that has been found to have an increased in functional connectivity in MdDS patients [25]. Taking this into account, neurochemical imbalances driven by hormonal changes may contribute to changes in functional connectivity [63]. Thus, investigating specific hormonal phases and the influences of such on neurotransmitters (e.g., plasma levels of GABA) in MdDS patients and in controls could further test this theory.

4. CGRP in MdDS Pathophysiology

As previously mentioned, there is a great interest in the role of CGRP with respect to migraine pathophysiology. Similarly, CGRP may also be relevant for MdDS and other vestibular disorders. CGRP is known to act at efferent synapses and their targets in auditory and vestibular hair cell organs, including the cochlea and vestibular end organs as well as the vestibular nuclei [71]. CGRP is also expressed in vestibular efferent neurons as well as a number of central vestibular neurons [72]. Luebke et al. reported that CGRP plays a role in ensuring VOR performance [72]. The study was conducted on mice with a targeted deletion of the αCGRP gene, and they displayed a marked decrease in vestibular function (50% reduction of VOR

gain). CGRP in addition was also observed to play a major role in the vestibular nuclei and cerebellum [71]. In a recent study, it was described that CGRP levels are influenced by hormonal fluctuations [48]. In another study by Valdemarsson [73], it was revealed that in healthy subjects immunoreactive CGRP (i-CGRP) plasma levels were significantly higher in females than in males, and that the use of combined contraceptive medication (i.e. containing estrogen and progesterone) was associated with even higher plasma levels of i-CGRP [48]. Similarly, it was observed that in postmenopausal women, decreased estradiol serum levels were positively correlated with decreased plasma i-CGRP concentrations, suggesting that the CGRP system can be directly influenced by endogenous or exogenous gonadal hormones [48].

Taking into account that hormones are predisposing factors for MdDS and that CGRP, as a G-protein coupled receptor may be influenced indirectly by GABA changes, it is possible to hypothesise that CGRP may be involved in MdDS pathophysiology. Thus, we postulate that neuromodulation through the agonist CGRP, which is currently under investigation for migrainous patients [74], may be significant for MdDS patients too.

5.Consequences of the hypothesis and future studies

We hypothesize that hormonal and neurochemical imbalances act as predisposing factors for developing MdDS. MdDS symptoms have been linked to changes in hormonal status, and the incidence of peculiar hormonal phases during onset suggests that gonadal hormones may be implicated in the symptomatology and pathophysiology of MdDS in female patients. Specifically, we theorize that patients who develop MdDS may have had, at the time when onset occurred, abnormal GABA and CGRP levels due to hormonal changes or the comorbidity of depression. Hormonally-regulated changes could potentially modulate the GABAergic system [75], as well as serotonergic system or other major neurotransmitters. Given the relevance of $GABA_b$ sensitive neurons implicated in the VOR maladaptation hypothesis and that drugs acting on GABAergic systems seem to be beneficial for MdDS patients, we propose that evaluating GABA plasma levels in MdDS patients may provide valuable insights into MdDS pathophysiology, especially with a follow-up that could assess patients also after a successful treatment. CGRP may also be involved in MdDS pathophysiology. This hypothesis can be supported by the fact that CGRP plays a role in ensuring the

functioning of the VOR [72], as well as their sensitivity to hormonal changes during menses [49]. Both systems are subject to hormonal modulation, and a change in their functioning could influence the VOR, thus enabling a VOR maladaptation.

More research is needed to test these theories. GABA plasma levels should be correlated with *in vivo* ^{1}H-MRS images, and patients should also be monitored after remission of symptoms to compare potential GABA changes pre and post interventions.

Future studies should focus on the hormonal influences on neurotransmitters (e.g. GABA) and how they correlate to MdDS symptomatology changes. As a result, these tests should be performed in different phases of the menstrual cycle in MdDS patients who are still in their reproductive years and should be also compared with gonadal hormonal blood sampling, which could provide additional information about the current hormonal profile of the subject, for example the estrogen withdrawal phase, during menses and ovulation. In addition, these parameters should also be compared with i-CGRP, relate them to hormonal parameters and to symptom scales. Gaining information about whether hormonal levels correlate with brain alterations found in MdDS patients and, perhaps more practically, whether further treatments or therapeutic options should take into consideration these hormonal fluctuations, may be of great relevance to ease MdDS symptoms and develop successful treatments. New studies could also evaluate if hormonal interventions can have any therapeutic potential, as well as the use of antagonist CGRP drugs, as observed in migrainous patients, could benefit MdDS subjects too. This new hypothesis could only be partially further tested with long term followed up, and by following patients with a multidisciplinary approach.

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Conflict of Interest Decleration

The authors declare to have nor ethical or economical conflict of interest to report.

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