FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

RESEARCH IN PATIENTS AFFECTED BY MAL DE DEBARQUEMENT SYNDROME

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Abstract (Dutch)

Doel: Deze studie beoogde om de voetafdruk van het Mal de Debarquement Syndroom (MdDS) te identificeren om zo een duidelijk beeld te verkrijgen van de onderliggende oorzaak van deze aandoening. Verschillende epidemiologische factoren zoals leeftijd, geslacht, het ontstaan van de aandoening en de co morbiditeit werden hiervoor in rekening gebracht. Ook de levensstijl (bv. werk, sociale leven, slaappatroon) van de deelnemers werd geanalyseerd om zo een beter overzicht te verkrijgen van de mate waarin MdDS het dagelijkse leven van de patiënten kan beïnvloeden.

Methode: Eenentwintig MdDS patiënten tussen de leeftijd van 24 en 71 jaar oud (gemiddelde leeftijd van 46.8 ± 11.6), namen deel aan dit onderzoek. Deze patiënten vulden ieder een epidemiologische vragenlijst in die focuste op de verschillende aspecten van MdDS. Elf van de deelnemers werden ook blootgesteld aan het VOR protocol, dit werd ontleend uit de studie van Dai, Cohen, Smouha & Cho (2014). Het resultaat van de behandeling werd geanalyseerd aan de hand van de score op de VAS (Visual Analog Scale).

Resultaten: Uit dit onderzoek bleek dat er meer vrouwen dan mannen betrokken waren bij deze studie. Wanneer de co morbiditeit van MdDS werd geëvalueerd, bleek alleen tinnitus significant aanwezig te zijn bij patiënten met MdDS. De meeste deelnemers bleken de ziekte te hebben ervaren na een blootstelling aan een passieve beweging (bv. op een boot of vliegtuig). Verder bleken bijna alle patiënten een opvallende vermindering van de symptomen waar te nemen wanneer ze (opnieuw) werden blootgesteld aan een passieve beweging. Hierbij was er een significant verschil waarneembaar in geslacht en het ontstaan van de aandoening. Als gevolg van deze ziekte bleken meer vrouwen dan mannen gestopt te zijn met werken. Ook de verschillende triggers werden onderzocht waarbij een significant verschil werd gedetecteerd op basis van de manier waarop de aandoening ontstond. Het analyseren van de behandeling, gebaseerd op het VOR protocol, resulteerde in een positief resultaat bij zeven van de elf patiënten. Namelijk, hoe groter de verbetering was op de VAS, hoe beter het resultaat van de behandeling was.

Conclusie: De online vragenlijsten leken een goede manier om meer informatie te verzamelen over de verschillende aspecten van MdDS. Omdat de studiegroep slechts bestond uit eenentwintig patiënten, zouden we dit onderzoek graag als een pilootstudie introduceren. Hierdoor dienen de verkregen bevindingen enkel als voorlopige resultaten te worden beschouwd en willen we verder onderzoek ten sterkste aanmoedigen. Door gebruik te maken van een grotere onderzoekspopulatie kan men mogelijk meer te weten komen over de onderliggende pathofysiologie van MdDS om zo deze zeldzame aandoening beter te kunnen begrijpen.

Abstract (English)

Objective: This study aimed to identify the footprint of the Mal de Debarquement Syndrome (MdDS) and to increase the current understanding of its pathophysiology. As a result, different epidemiological factors such as age, gender, onsets and associated co-morbidities were taken into account. In addition to this, the lifestyle aspects of the MdDS patients were also considered (e.g. employment, social life, sleeping patron) in order to assess how much MdDS is impairing the patients' life.

Methods: Twenty one MdDS patients between 24 and 71 years old (mean 46.8 ± 11.6 years), participated in this study. They filled in an epidemiological questionnaire focussing on different features of MdDS. Eleven of them were also exposed to the VOR-protocol derived of the study of Dai, Cohen, Smouha & Cho (2014). The treatment outcome has been analysed using the VAS (Visual Analog Scale).

Results: Considering the gender distribution, more female than male patients were involved in this study. The patients indicated a wide range of symptoms; especially rocking, swaying and/or bobbing, which were reported to be constant. Taking a look at the co-morbidity of MdDS, only tinnitus has been found to be significantly present in patients with MdDS. Evaluating the onset of the disease, most patients appear to experience a motion triggered onset. Almost all of the patients were indicating a remarkable relief of symptoms when being (re)-exposed to passive motion. Regarding this aspect, a significant difference in gender and onset has been found. Evaluating the influence of MdDS on the patients' lifestyle, it has been observed that more female than male patients left their job. Considering MdDS triggers, a significant difference based on the onset of the condition has been found. Also, in this study the VOR protocol from Dai, Cohen, Smouha & Cho (2014) was reproduced and it resulted in a positive outcome in seven of the eleven patients, based on the improvement on the VAS (Visual Analog Scale).

Conclusion: In summary, the use of online questionnaires proved to be a good and efficient way to collect information about the various features of MdDS. As the study sample only consisted of twenty one patients, these findings can only be considered preliminary. The VOR protocol only provided limited data as only eleven subjects were considered, therefore we would like to introduce this research as a pilot-study. As a result, we encourage to continue the investigation involving a larger number of patients.

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1 Introduction

In 1881, J.A. Irwin discovered a condition characterised by a loss of balance as a result of a vestibular adaptation to sea conditions (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). The feeling of unsteadiness that can take place after disembarking from a boat, is now a well-known phenomenon which has been described before in the literature as sick of disembarking, Mal de Debarquement (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). It normally disappears after 48 hours (Gordon, Spitzer, Doweck, Melamed & Shupak, 1995). However, in some cases it can last up to months or years (Cha, Cui & Baloh, 2013). When this occurs, we talk about the Mal de Debarquement Syndrome (MdDS) (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015).

While considering this condition, a distinction has to be made between persistent MdDS and transient MdD symptoms (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). As mentioned in the literature, the Mal de Debarquement Syndrome (MdDS) has a duration of 3 days up to several years and is considered to be a pathological condition (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008; Brown & Baloh, 1987). It has a wide range of associated symptoms and can seriously affect the patients' quality of life (Clark et al., 2013; Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). For now, MdDS is considered to be a poorly understood disorder, as the real aetiology is still unknown. The condition is characterised by a continuous feeling of internal swaying, rocking and/or bobbing (Clark et al., 2013; Cha & Chakrapani, 2015). MdDS' main feature is a constant and chronic self-motion perception (Clark et al., 2013). The onset is usually occurring after the exposure to passive motion (e.g. travelling on a boat, plane or train) (Dai, Cohen, Smouha & Cho, 2014). However, in some cases, the symptoms can also appear spontaneously (spontaneous onset) (Dai, Cohen, Smouha & Cho, 2014).

The review by Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts (2015) reported a list of the symptoms associated with MdDS, such as disorientation, postural instability, imbalance, fatigue, cognitive fatigue and kinesiophobia.

Some otological symptoms (fullness of the ears, tinnitus, hyperacusis, otalgia and hearing loss), neurological symptoms (nausea, headache, perioral tingling, tilting, spinning, numbness in foot or leg) and symptoms with visual disturbance (jumping vision, blurred vision, diplopia, eye twitches) were also mentioned as possible additional symptoms (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). One study by Clark et al. (2013) observed that patients with MdDS exhibit impaired postural control, along with high levels of kinesiophobia and fatigue. Also, a positional nystagmus was noted in a research by Brown and Baloh (1987) and Murphy (1993). Nevertheless, it does not necessarily mean that all of these symptoms are evenly associated with MdDS (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015).

MdDS is considered a rare disorder (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). It is still unclear how many patients are suffering from this condition, given that it is often misdiagnosed or undiagnosed (Clark & Quick, 2011). Many cases of MdDS are being misdiagnosed as other disorders, often because the relevant clinical history of the motion trigger has not explicitly been sought (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). It has been reported by MacKe, LePorte & Clarck (2012) that, on average, an MdDS patient goes through 19 visits to a healthcare professional before receiving the diagnosis of MdDS. In addition, there are no clear diagnostic criteria and MdDS is currently diagnosed by exclusion of other possible conditions (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). Therefore, this current research aimed to make a clear overview of the different symptoms and associated features characterising MdDS patients.

As the underlying mechanism of MdDS is unknown, the actual prevalence of the disease is still unclear. However, in the investigation by Hain T. C. (2017), it is thought to be 0.05%. This means that 0.5 per 1000 persons would suffer from this disease. Research by Hain, Hanna & Rheinberger (1999) showed that MdDS has a mean duration of 3.5 years with a standard deviation of 2.5 years. However, a prospective study would be necessary to answer this question properly (Hain, Hanna & Rheinberger, 1999).

In the review paper of Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts (2015), it has been mentioned that MdDS is most probably a condition which doesn't originate from vestibular dysfunction as vestibular tests are normal. Most patients also have normal or non-specifically abnormal neurological exams, electronystagmography (ENG) and (Anatomical) Magnetic Resonance Imaging results (MRI) (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). As a result, the clinical neurological and oto-vestibular exams are not used to diagnose MdDS patients (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). Therefore, it is obvious that there is an extreme need for developing clear diagnostic criteria and to raise awareness among health care specialists (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015).

As described before, the underlying pathogenesis of MdDS is not clearly understood at this stage (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). However, different hypotheses were put forward. Dai, Cohen, Smouha & Cho (2014) hypothesised that MdDS is the result of a maladaptation of the vestibulo-ocular reflex (VOR). According to this research, the VOR adjusts to the new pattern of motion while travelling at sea, but when returning to land, the reflex fails to adapt itself (Dai, Cohen, Smouha & Cho, 2014; Saltsman, 2014).

On the other hand, according to another research line, MdDS was considered to be a disorder of neuroplasticity and sensory reorganisation (Cha, Chakrapani, Craig & Baloh, 2012). Recent neuroimaging studies have provided more insight about potential features that unite MdDS patients (Cha Y. H., 2015). In the investigation by Cha, Chakrapani, Craig & Baloh (2012) changes in structural, functional and metabolic brain properties were reported. In this study, individuals with MdDS showed brain volume differences from healthy controls. In particularly, metabolic changes in circuits related to vision, vestibular processing and emotional reactions were found. The study assumed that the brain volume and the duration of illness were related. Based on these findings, MdDS is now considered to possess a neurological component (Cha, Chakrapani, Craig & Baloh, 2012).

Regarding MdDS onsets, there are different conditions to be taken into account. In most cases, the MdDS symptoms are provoked by different forms of passive motion (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015), for example being a passenger on a plane, train or boat (Cha Y. H., 2009).

While air and land travel has been reported as a possible trigger, sea travel has been described as being the most prevalent trigger (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015; Cha Y. H., 2009). However, as mentioned before, some MdDS patients are also reporting a spontaneous onset (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). In this case, the symptoms can occur abruptly and the patients can simply wake up with MdDS (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). In this current research, different forms of onset have also been taken into account.

When contemplating the motion triggered onset of MdDS, it is still not clear how long the exposure is in most of the MdDS cases (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). The information presented in the existing literature is often confusing (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). A study by Cha, Cui & Baloh (2013) has reported that the duration of the passive motion event should have a minimum period of 2 hours. On the other hand, the research by Hain, Hanna & Rheinberger (1999), described that the minimum exposure to passive motion should have a duration of 4 hours. As a result, there are no standard data concerning the minimum exposure to passive motion (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015).

In the study by Cha Y. H. (2015) an interesting factor has been noticed which is exclusive for MdDS patients. Regardless the MdDS onset (spontaneous or motion triggered onset), patients are often experiencing a full remission of symptoms when being (re)-exposed to passive motion (Cha Y. H., 2015). In the study by Sharon & Hullar (2014), it has been described that most of the MdDS patients are getting better when they are driving a motor vehicle, some of them were even noticing a remarkable relief of their symptoms when just being a passenger in a car. This varies from the situation with patients suffering from Meniere's disease (MD) or vestibular migraine (VM), who generally get worse in those conditions (Sharon & Hullar, 2014).

Another interesting finding that has been previously observed, is that the majority of the MdDS patients are females (Van Ombergen, Wuyts & Cha, 2016). Several studies noted this female predominance, however it is still unclear what is the cause of this gender distribution (Clark et al., 2013).

Age of onset is typically considered between 40 and 50 years old, this has been confirmed by multiple studies. (Cha Y. H., 2015; Arroll, Attree, Cha & Dancey, 2014). As a result, this study aimed to investigate the distribution of age and gender in patients suffering from MdDS.

As described in the previous epidemiological data, MdDS is gender driven (Van Ombergen, Wuyts & Cha, 2016). As a result, this research aimed to focus on evaluating the hormonal components in female MdDS patients. In the existing literature, it has already been highlighted that hormones play an important role in various vestibular pathologies such as vestibular migraine (VM), and Meniere's disease (MD) (Pearce, Davies & Major, 2015). A potential correlation between hormonal fluctuations and various inner ear symptoms such as vertigo, instability, tinnitus, hearing loss and intra-aural pressure, has been previously described in a study by Andrews, Ator, & Honrubia (1992) and Zigmond & Snait (1883). In the research by Hain, Hanna & Rheinberger (1999), it has been demonstrated that the majority of the female individuals were either premenopausal or receiving hormone replacement therapy. While, in the investigation by Dr. Hain T. C. (2017), it has been illustrated that many female patients developed MdDS when being exposed to motion during their menstrual cycle and that they were also more prone to develop migraine. Further investigations are needed to address potential hormonal components related to MdDS. Therefore, the current research aimed to gather more information about the possible hormonal influence on the development of MdDS in female patients.

Individuals with MdDS spend significant time, energy and money trying to be diagnosed and treated (Cha Y. H., 2015). As a result, high levels of depression and anxiety are often observed in MdDS patients (Cha Y. H., 2015). It has been previously described by Clark et al. (2013) that people with MdDS report a poor quality of life, as assessed through the Quality of Life (QOL) scale. One of the main reasons is that in many cases, there is a long period of time between the onset of the symptoms and the moment when the patient is appropriately diagnosed (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). The visit of multiple doctors without having a clear diagnosis can lead the patient to develop secondary mood disorders such as depression and anxiety (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015).

In the research by Kurre, Straumann, Van Gool, Gloor-Juzi & Bastiaenen (2012), it has been noticed that 26% of the female patients that considered their condition, characterised by dizziness, unsteadiness and vertigo, to be very severe, also experienced anxiety. 19% of them mentioned to have a depression. In men, 60% noticed having anxiety, 66,7% of them suffered from depression. Given those preliminary studies, this current research aimed to investigate the underlying prevalence of anxiety and depression in MdDS patients.

Some of the MdDS patients are also affected by tinnitus and migraines, which are also well known pathologies to have negative psychological effects (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015; Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). Consequently, it is now clear that MdDS has a significant socio-economic impact. A lot of patients have to quit their jobs due to MdDS (Clark et al., 2013). Considering this, the current investigation also aimed to quantify how much MdDS can impair the patients' lifestyle, taking into account the patient's quality of life.

It has been observed before that MdDS patients have a higher prevalence of migraine than the standard population, especially patients with a spontaneous onset of the condition (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). In addition to this, both conditions have been shown to have a female preponderance (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015; Brown & Baloh, 1987; Murphy, 1993). Taking into account that there are more female MdDS patients (Van Ombergen, Wuyts & Cha, 2016) and that migraine is also more prevalent in women (Talarska, Zgorzalewicz-Stachowiak, Michalak, Czajkowska & Hudaś, 2014), migraine and MdDS might have a pathophysiological overlap (Cha Y. H., 2015).

The relationship between migraine and spontaneous versus motion-triggered episodes of MdDS has been investigated recently by Dr. Cha Y. H. (2015). He concluded that, after the onset of MdDS, both spontaneous and motion triggered patient groups had a similar prevalence of headache meeting the criteria for migraine. However, in a previous research by Cha, Brodsky, Ishiyama, Sabatti & Baloh (2008), it was reported that patients with a spontaneous onset had a much higher rate of migraine than those with motion triggered MdDS. This finding has been reconfirmed by Dr.Cha in a later study (Cha Y. H., 2015).

Knowing more about the migraineous component of MdDS would allow clinicians to improve clinical practice. In the study by Ghavami et al. (2016), it has been noticed that management of MdDS as vestibular migraine can improve the patients' symptoms and increase the quality of life (QOL). In that study, nearly all the patients suffering from MdDS had a personal or family history of migraine headaches or had signs or symptoms suggestive of atypical migraine (Ghavami et al., 2016). In the investigation by Mauskop (2012), it also has been noted that most of the patients with MdDS suffer from headaches and frequent migraineous attacks as well. However, a larger study cohort is definitely needed to reconfirm this knowledge.

While assessing MdDS, several studies investigated if MdDS patients are also more prone to be suffering from motion sickness prior the onset of the condition (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015). Various studies assumed that the relationship between both entities is based on the underlying problem in both conditions, namely a maladaptation on land after an exposure and simultaneous adaptation to motion (Kurre, Straumann, Van Gool, Gloor-Juzi & Bastiaenen, 2012; Murphy, 1993).

Positive correlations were reported, but the associations appear not to be direct (Cha Y. H., 2015). In a recent investigation by Cha Y. H (2015), it has been reported that MdDS is possibly a disorder of poor adaptation to stable conditions after a period of adaptation to motion. Accordingly, the correlation between the development of seasickness and the subsequent development of MdDS were assessed by Dr. Cha (Cha Y. H., 2015). This study showed that the tendency to develop post-sailing dizziness and the exposure to seasickness, seem to correlate with a lack of experience to sea travels (Cha Y. H., 2015). It is possible, as confirmed by different research groups, that MdDS and motion sickness may share a common link (Tal, Wiener & Shupak, 2014; Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). However, it is still not clear how many MdDS patients with spontaneous onset may be suffering from motion sickness. As a result, the current research took into account motion sickness and assessed how many MdDS patients, with both onsets, were affected.

Taking into account these observations, this study aimed to evaluate the presence of different co-morbidities among MdDS patients with different onsets (motion triggered-spontaneous). Knowing if MdDS patients were already more susceptible to motion or migraine, could help to characterise MdDS patients' vulnerabilities.

The current study also aimed to consider the presence of Monosodium Glutamate (MSG). This substance, which is often added to canned vegetables, processed meats, soups and Chinese food, works as a flavour enhancer (Xiong, Branigan & Li, 2009). The American Food & Drug Administration (FDA) has received a lot of reports of adverse reactions to food containing MSG. People were mentioning symptoms such as headache, flushing, sweating, facial pressure, numbness, chest pain, nausea and weaknesses (Xiong, Branigan & Li, 2009).

A case study by Xiong, Branigan & Li (2009) reported that absence of MSG in food led to a decrease of headache. According to this results, this current research would like to evaluate how many MdDS patients are eating MSG and if this can possibly lead to any aggravation of symptoms.

Aside from associated co-morbidities, another important aspect of MdDS are the current treatment options. It is known that in multiple cases MdDS can resolve spontaneously (Cha Y. H., 2015). But for the one that don't, the treatment options are extremely limited for now.

As mentioned before, the study by Cha, Chakrapani, Craig & Baloh (2012) reported an association between resting state metabolic activity and functional connectivity between the entorhinal cortex and amygdala in a human disorder of abnormal motion perception. After the neuroimaging analysis, given the neuroimaging finding, neuromodulation was then taken into consideration (Cha, Chakrapani, Craig & Baloh, 2012). This study by Cha, Chakrapani, Craig & Baloh (2012) created a specific protocol for MdDS patients using Repetitive Transcranial Magnetic Stimulation (rTMS).

Another therapeutic option, which has provided positive results for now, is the protocol developed by Dai, Cohen, Smouha & Cho (2014), also named the VOR protocol. Dai and colleagues, as previously reported, considered MdDS to be the result of a maladaptation of the vestibulo-ocular reflex (VOR) (Dai M. , Cohen, Smouha & Cho, 2014).

This maladaptation could be modulated by providing a full-field optokinetic stimulus in combination with a certain movement of the head (Dai, Cohen, Smouha & Cho, 2014). The study by (Dai M., Cohen, Cho, Shin & Yakushin, 2017) noticed that, after a week of treatment, the initial rate of significant improvement was 78% in patients with a motion triggered onset and 48% in patients who indicated a spontaneous onset of the condition. One year later, a significant improvement has been found in 52% of the subjects with a motion triggered onset and 48% of the patients with a spontaneous onset. 27% of motion triggered and 19% of spontaneous patients indicated a complete remission of symptoms. Most patients reported fewer and milder symptoms than before. Although, half of the patients did not achieve a 50% improvement. This results made this treatment very promising (Dai M., Cohen, Cho, Shin & Yakushin, 2017). In the Antwerp University Research centre for Equilibrium and Aerospace (AUREA), the VOR protocol was reproduced and MdDS patients with motion and spontaneous onset were assessed.

In summary, MdDS is a rare and debilitating disease with an unclear aetiology, associated co-morbidities and treatment options which are still being investigated. The research in this paper aimed to gather more information about the underlying pathophysiology of MdDS. This study involved two sections:

1) An epidemiological study where MdDS patients were enquired via online surveys, in order to gain a greater number of patients;

2) A detailed assessment of MdDS patients at the Antwerp University Research centre for Equilibrium and Aerospace (AUREA) where these patients were exposed to the VOR protocol.

Taking into account what has been done in the MdDS research field, this current study aimed to identify the footprint of the Mal de Debarquement syndrome (MdDS) and to assess the different features of MdDS considering epidemiological factors such as age, gender, onsets and co-morbidity with other (vestibular) disorders. Additionally, this research investigated the presence of potential triggers, medication and food as these factors might have an impact on the severity of the condition. By evaluating the patients' employment, social life and sleeping patron, this research intended to investigate how much MdDS can impair the patients' lifestyle. Therefore, the occurrence and fluctuations of symptoms were also taken into account.

By investigating the most common aspects of the condition, it might be possible to get a clearer view about the cause of the Mal de Debarquement Sydrome. Therefore this research set out the following hypotheses:

- Considering the age and gender distribution, this study assumes that there will be more female than male patients, aged 40 to 50 years old;
- Evaluating the menstrual cycle in female MdDS patients, this research suspects that there is a hormonal influence on the development of MdDS;
- Taking a look at the onset of the condition, differentiating spontaneous onset from motion triggered onset, this current research assumes that the amount of patients will be evenly distributed between those two categories;
- This study expects an association of MdDS with migraine, motion sickness, depression, anxiety, tinnitus and possibly other (balance) disorders, meaning that more MdDS patients will report associations with one or more of these (vestibular) conditions;
- Considering the impact of MdDS on the patient's lifestyle, this current research assumes that there could be an influence of medication, food and specific triggers on the daily life of MdDS patients. MdDS subjects may report disrupt sleeping patterns, lack of social interactions and loss of employment after the syndrome onset;
- Looking at the occurrence of the patients' symptoms, this study expects the patients to have a constant feeling of certain typical MdDS symptoms. Possible fluctuations of symptoms, often caused by specific triggers, are also believed to be part of MdDS.

2 Methodology

2.1 Subjects

The current research was conducted in the Antwerp University Research centre for Equilibrium and Aerospace (AUREA) in the Antwerp University Hospital (UZA, Belgium). The research protocol was approved by the ethical committee from the Antwerp University Hospital (UZA, Belgium) (Ethical number: 15/44/454) and from the University of Ghent (Belgium) (Ethical number: B670201630419).

Patients recruitment:

21 patients, diagnosed with Mal de Debarquement Syndrome (MdDS), were recruited to fill in the MdDS survey. The group contained 6 males, 15 females, ranging in age from 24 to 71 years old with a mean age of 46.8 and a standard deviation of 11.6.

11 patients were diagnosed during vertigo-specific consultations in the department of Ear Nose and Throat diseases at the Antwerp University Hospital (UZA, Belgium). The recruitment has been supervised by Prof. Dr. Van de Heyning, Prof. Floris Wuyts and Prof. Dr. Vincent Van Rompaey.

The other 10 patients were re-directed by other colleagues to AUREA or were recruited by advertisement in patient-forum groups (closed facebook groups created by members of the UK Patient Support Group for MdDS). Those patients were diagnosed by an Ear Nose and Throat doctor in their own country according to the inclusion criteria.

Only when a patient met the inclusion criteria, he/she was asked to participate in the study. At this stage, the patient received explanatory information about the motivation and content of the research. The patient had more than 24 hours to evaluate the participation to the study and to sign the informed consent form[1].

[1] Reference to appendix

Study size

The research aimed to include 30 patients in the study. However, considering the research time constrain and the fact that MdDS is a rare disorder, only 21 patients were recruited. As a result, we would like to consider this current research to be a pilot-study. We think this number is not sufficient comparing previous studies concerning MdDS (e.g. Dai, Cohen, Smouha & Cho, 2014). Depending on the results obtained by this research, a new study can be set up.

Nationalities:

From the 21 patients recruited, 8 of the patients had a Belgian nationality, 3 of them were Australian. The other patients were born in France, Israel, Swiss, Hungary, America (North Carolina), the United Kingdom and the Netherlands.

2.2 Diagnostic guidelines

Due to the absence of clear-cut diagnostic criteria for MdDS, the diagnostic guideline developed by (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015) was used as inclusion criteria. The inclusion criteria were different for patients with a spontaneous onset of the condition.

Inclusion criteria motion triggered MdDS:

a) Chronic perception of rocking dizziness (e.g. rocking, bobbing, swaying) that started after passive motion such as sea, air and land travel;

b) Symptoms lasting at least 1 month;

c) Normal inner ear function or non-related abnormalities as seen by ENG/VNG and audiological tests;

d) Normal structural brain imagining or non-specific alterations with a non-contrast MRI scan (when no additional analysis were carried out);

e) Symptoms that cannot be taken into account for a different diagnosis made by a physician.

Inclusion criteria spontaneous MdDS:

The research team was aware that this preliminary guideline was not taking into account MdDS patients with spontaneous onset or with other onsets. Patients reporting MdDS symptoms without the initial exposure to passive motion, were identified by our team as MdDS patients when they reported option b, c, d and e from the above table and when they had a full remission or a great improvement of their symptoms when being re-exposed to passive motion (e.g. when being a passenger in a car).

Exclusion criteria:

a) Patients < 18years;

b) Patients suffering from epilepsy;

c) Patients having visual impairments that cannot be corrected with glasses or contact lenses;

d) Pregnant women.

2.3 Study material

The current research was carried out by using an epidemiological questionnaire[2]. This questionnaire consisted of 25 open questions and an extra space to write additional comments.

In order to find an answer on the research questions, this questionnaire was focussing on the patients' clinical history, the onset of the disease, symptoms, gender, age, and co-morbidity in patients with MdDS.

The first questions considered the onset and the diagnosis of the condition. If the patients were indicating that the onset of their condition was motion triggered, they were asked which motion event could have triggered the rocking dizziness (e.g. a cruise, an airflight). In this way, a clear distinction could have been made between the different motion events triggering the MdDS symptoms. Following questions were focussing on the clinical history of the patient. Thus, it was possible to get a complete medical record of the patients.

[2] Reference to appendix

For women there was an extra part about their gynaecological history where they were asked about their contraceptive, period and menopause with the aim of gathering some more information about the hormonal component in the development of MdDS.

Furthermore, the questionnaire considered the occurrence and fluctuation of the symptoms. Re-exposure to passive motion was also taken into account, as in previous studies it has been mentioned that this could lead to relief of symptoms.

Additionally, the questionnaire considered how MdDS might impair the patients' lifestyle. As a result, the list consisted questions concerning the social life of the person, hours of sleep and the patients' employment. Also, the subjects were asked about some specific triggers that could be aggravating the symptoms. For example alcohol, stress and changing weather were taken into account. Furthermore, the patients' living habits were evaluated. The questionnaire was asking about eating any food containing Monosodium glutamate (MSG), the patients' smoking history and medications, in order to detect if these features could have any influence on the development of this condition. The patients were also asked about the severity of their symptoms, which could be indicated on a severity-scale between 0 and 10. (0- symptoms free, 5- moderate, 10- most severe).

Lastly, the study considered the success rate of the VOR protocol. The study was conducted in the Antwerp University Hospital (UZA, Belgium) and involved 11 MdDS subjects (mixed onset).These patients were exposed to the vestibulo-ocular reflex (VOR) re-adaptation protocol of Dai, Cohen, Smouha & Cho (2014). Similarly to the study mentioned above, this current treatment was based on the hypothesis that VOR re-adaptation will restore the potential maladaptation, leading to an overall reduction of symptoms in MdDS patients. The treatment set up will be explained below.

2.4 Treatment method

The treatment method was based on the study of Dai, Cohen, Smouha & Cho (2014).

Duration:

The treatment was performed on 5 consecutive days. The patients received 5 sessions of treatment, one per day. A session lasted 45 minutes, including questionnaires and measuring parameters. Female patients were not treated during their menstrual cycle due to the possible aggravation of symptoms.

Sessions Structure:

Before starting the treatment, the patients' frequencies of oscillations were recorded during the posturography measurements by using a Wii Balance board©. During the treatment, the patient was seated in a chair in a darkened room, especially built for the experiment. A full-field optokinetic visual stimulus was projected with a certain constant speed, while the head was rolled at about 20° per second based on the frequencies of oscillations found during the posturography measurements. The head was rotated by one of the researchers on the team, who was standing behind the patient and moved the head guided by the frequency of a present metronome.

Standard Stimulation:

Optokinetic vertical stripes were exposed to the patient, at a rate of 10°/sec with a moving direction to the left or right, depending on the observations of the patient. Meanwhile, one of the team researchers moved the head simultaneously in the roll plane about 20° at a frequency of 0.165 Hz.

Variations of the stimulus:

Variations were possible within the parameter settings, similar to the study by Dai, Cohen, Smouha & Cho (2014).

- Frequency of head roll: 0.01 Hz - 0.7 Hz
- Direction of optokinetic stimulus: left versus right
- Velocity of optokinetic stimulus: 5 °/sec - 10 °/sec
- Duration of treatment: 30 seconds to 5 minutes
- Direction of head movement: rolling movement fixed versus non fixed

Before and after every session, the patients were asked to fill in an extra questionnaire[3] containing the VAS (Visual Analog Scale)[4]. This scale was used to detect how the symptoms were changing from the onset of the condition and could help to modulate the following trials. By making a comparison between the VAS score before and after the session, the outcome of the treatment could be evaluated. This questionnaire was also focussing on the past medical history, family history and social history of the patients.

[3] [4] Reference to appendix

2.5 Statistical analysis

Statistical analysis was performed using IBM SPSS Version 23.0. As the study sample was not sufficient, we have been working with non-parametric tests only. When performing the analyses, $p < 0.05$ was used as criteria for statistical significance.

As this research contained many nominal measurement levels, most of the data could be processed using the Chi-Square-test. This unpaired cohesion test allowed to explore whether two nominally measured variables were associated (Deschepper, Buysse & Coorevits, 2016). This test was used for example when investigating the possible co-morbidity from MdDS with other (vestibular) disorders (e.g. migraine, motion sickness, depression, tinnitus, anxiety/stress, sleeping problems).

The different features of MdDS were often distinguished based on gender and onset, which is another reason why this test was used. Furthermore, the Chi Square test was used for the statistical analysis of the motion event, menopause, menstrual cycle, contraceptive, drugs and medication when travelling, treatment outcome, employment, relief in passive motion and triggers.

The dataset also contained some continuous variables. When MdDS' features were for example distinguished based on age, duration of symptoms, severity scale or ΔVAS, the Mann-Whitney U-test was used for the statistical analysis. This non-parametric test is able to make a comparison between two unpaired samples, containing continuous data (Deschepper, Buysse & Coorevits, 2016).

When investigating if there was a significant difference in VAS-score comparing pre- and post-treatment, we used the Wilcoxon matched-pairs signed-ranks-test. This non parametric test makes a comparison of two paired samples and is looking for a significant difference. (Deschepper, Buysse & Coorevits, 2016)

3 Results

3.1 Age & Gender

Considering the gender distribution in the study group, the Chi-Square-test demonstrated a significant difference between male and female patients (p = 0.05). In this research, more female than male subjects were involved (Figure 1).

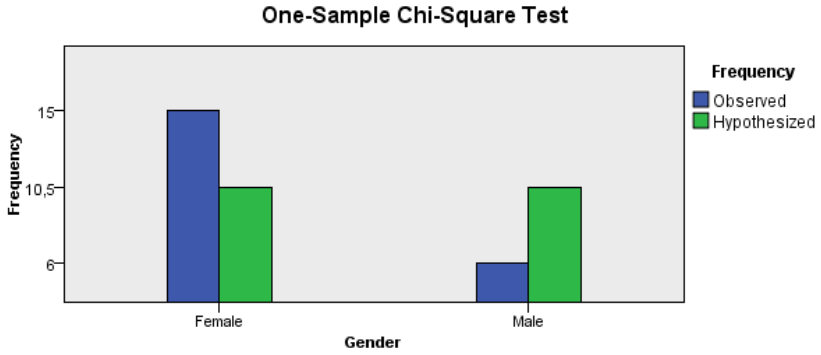

Figure 1: Bar chart of the gender distribution in the study population. The hypothesised number of subjects, differentiating on gender, was compared to the observed amount of subjects.

When considering the distribution of age in the study population, a mean value of 46.8 was obtained with a standard deviation of 11.6 (Figure 2). The minimum age was 24, while the maximum age was 71. Subsequently, the distribution of age based on gender has been analysed (Figure 3). However, the Mann-Whitney U-test demonstrated that there was no significant difference in age based on gender (p = 0.311).

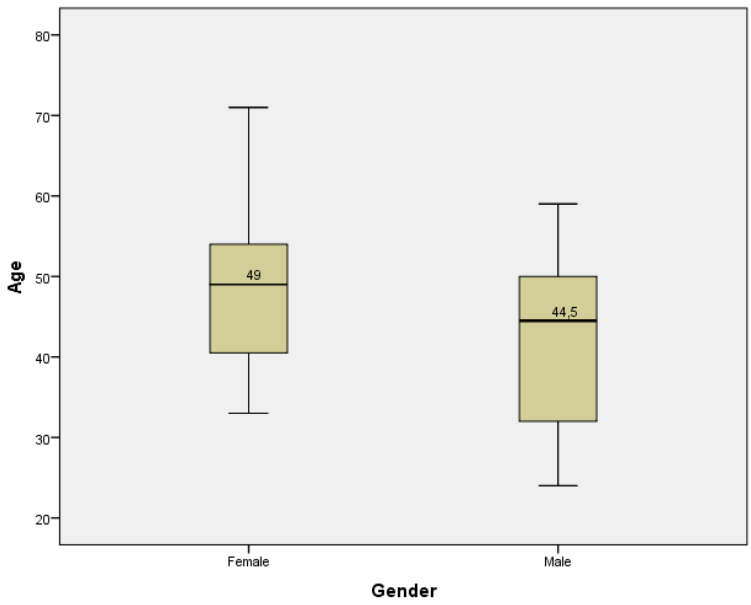

Figure 2: Boxplots representing the median age, based on gender.

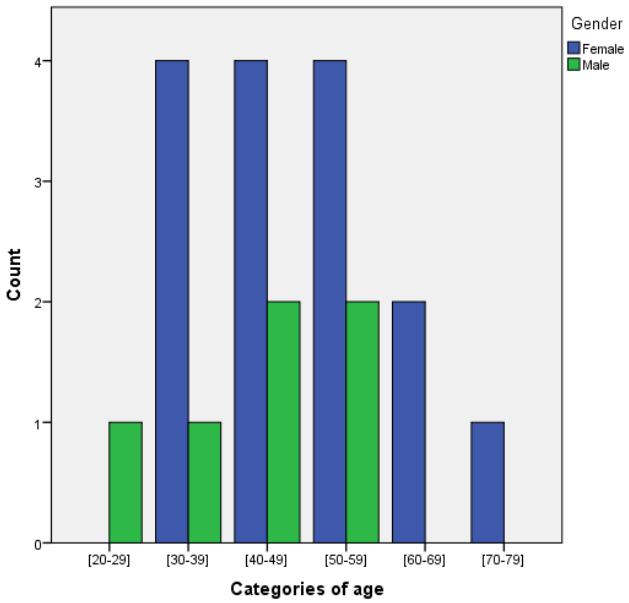

Figure 3: Bar chart of the gender distribution by categories of age. However, no significant difference in age based on gender was obtained. Looking at this bar chart, the categories [30-39], [40-49] and [50-59] most often occur in this study population.

3.2 Symptoms

The patients indicated a wide range of symptoms. The most common symptoms were:

- Rocking, swaying and/or bobbing;
- Head pressure;
- Nausea;
- Sensation of movement while standing/laying still;
- Fatigue;
- Balance disturbance, instability;
- Disorientation.

The occurrence and fluctuation of symptoms was also taken into account (Figure 11,12). All of the 21 patients were indicating a fluctuation of symptoms, especially when being exposed to specific triggers (Table 7). 16 patients were experiencing a constant feeling of symptoms; especially rocking, swaying and/or bobbing were named to be constantly present.

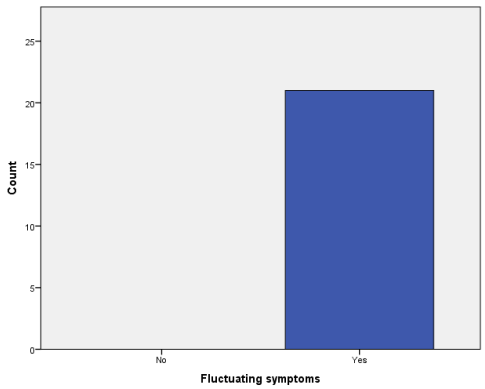

Figure 11: Bar chart of patients experiencing fluctuating symptoms.

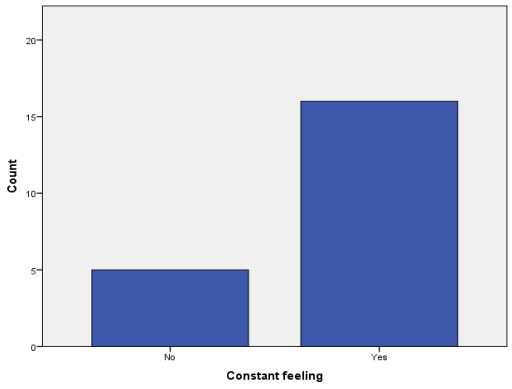

Figure 12: Bar chart of patients experiencing a constant feeling of symptoms.

3.3 Onset of the disease

Subsequently, the onset of the condition has been assessed. Firstly, the duration of the symptoms was analysed. The period of time was expressed in months. There was one missing value among all the patients, this case was excluded (the patient was not able to remember precisely when the symptoms started). A minimum duration of 5 months was indicated, with a maximum time period of 211 months (ca. 17.5 years). This resulted in a mean duration of 59.45 months (ca. 5 years) and a median of 36.50 months (ca. 3 years) (Figure 4).

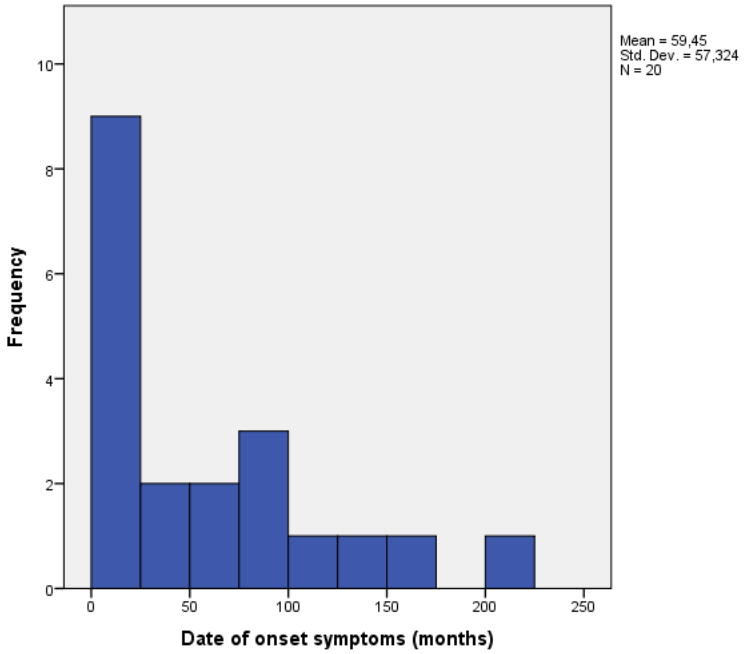

Figure 4: Bar chart representing the duration of symptoms in months. Most of the patients of this study population have been suffering from this condition for [0-25] months.

When evaluating the onset of the condition (motion triggered versus spontaneous onset), a significant difference has been found (p = 0.05). There was a greater number of patients reporting a motion triggered onset (Figure 5).

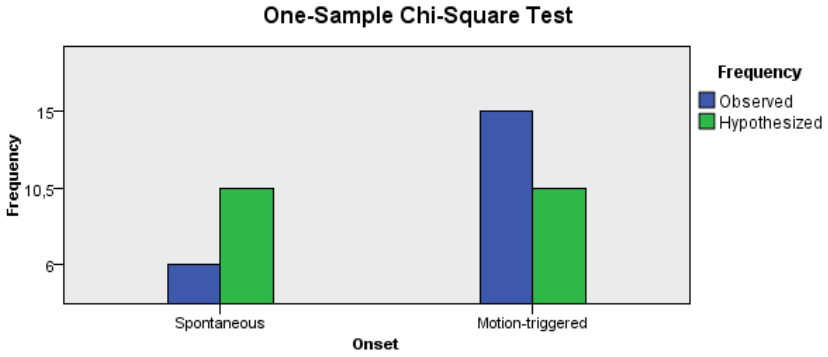

Figure 5: Bar chart of the onset distribution in the study population. The hypothesised number of subjects, differentiating on onset, was compared to the observed amount of subjects.

When analysing the categories of onset based on age (p = 0.907) and gender (p = 0.760), no significant difference was obtained. Meaning that the distribution of age and gender was equal concerning the onset of the condition. When differentiating the motion events that triggered the symptoms, no significant difference could have been found between air and sea travel (p = 0.439).

3.4 Hormonal component

Considering the presence of a hormonal component in the development of MdDS in female patients, menopause, contraceptive and menstrual cycle have been taken into account. The one sample Chi-Square test demonstrated a significant difference in stage of menopause (p = 0.041). The test showed that most of the female MdDS patients didn't reach menopause yet (Figure 6).

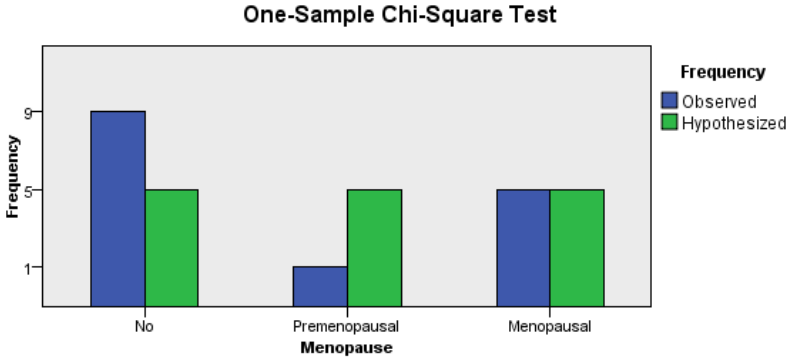

Figure 6: Bar chart representing the categories of menopause of the female subjects of the study population. The hypothesised number of subjects, differentiating on categories of menopause, was compared to the observed amount of subjects.

Evaluating the menstrual cycle in female patients, there was a significant difference too (p = 0.007). This information was only obtained from the women who indicated a motion triggered onset of the condition. More motion triggered female patients indicated they didn't have their menstrual cycle during the motion event (Figure 7).

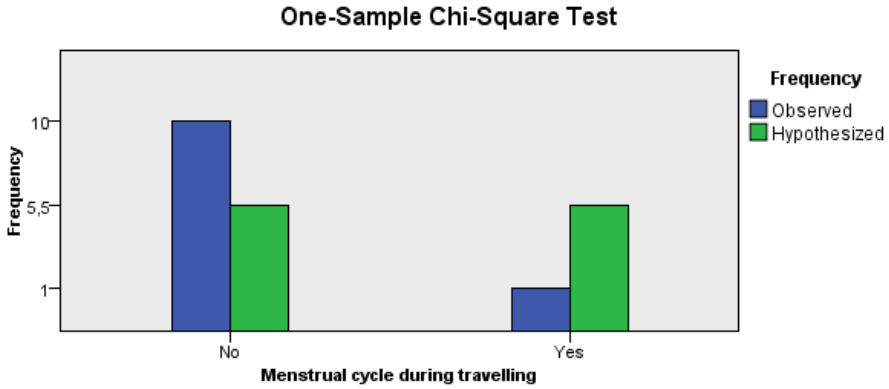

Figure 7: Bar chart representing the menstrual cycle of the female subjects of the study population. The hypothesised number of subjects, differentiating on menstrual cycle, was compared to the observed amount of subjects.

When looking at the possible influence of contraception, there has not been found a significant difference between no contraceptive, taking the pill, and having a hormonal spiral (p = 0.368). In the analysis, there were two missing values as two women didn't fill in the part of contraception.

3.5 Co-morbidity

Considering the co-morbidity of MdDS with other (vestibular) disorders, the following results have been obtained. The different disorders were analysed based on age, gender, onset and the prevalence of the condition in the population. (Table 1).

Table 1: Representing the co-morbidity of MdDS with other (vestibular) disorders.

p – value	Population	Age	Gender	Onset
Migraine	p = 0.197	p = 0.340	p = 0.445	p = 0.760
Motion sickness	p = 0.334	p = 1.000	p = 0.776	p = 0.088
Depression	p = 0.457	p = 0.762	p = 0.105	p = 0.517
Tinnitus	p < 0.001	p = 1.000	p = 0.577	p = 0.577
Anxiety/stress		p = 0.897	p = 0.292	p = 0.861

The first column represents the difference in prevalence with the standard population. When considering the co-morbidity of MdDS with migraine, the data was only obtained from the female patients, as the existing literature noticed a female preponderance for the co-morbidity between MdDS and migraine. However, no significant difference could have been noticed between MdDS and migraine. This was also the case with motion sickness and depression. Considering the co-morbidity between tinnitus and MdDS, a significant difference was obtained ($p < 0.001$). Compared to the population prevalence, a significant part of the MdDS patients has tinnitus.

There were no significant differences obtained between MdDS and the different vestibular disorders based on age, gender and onset (Figure 8).

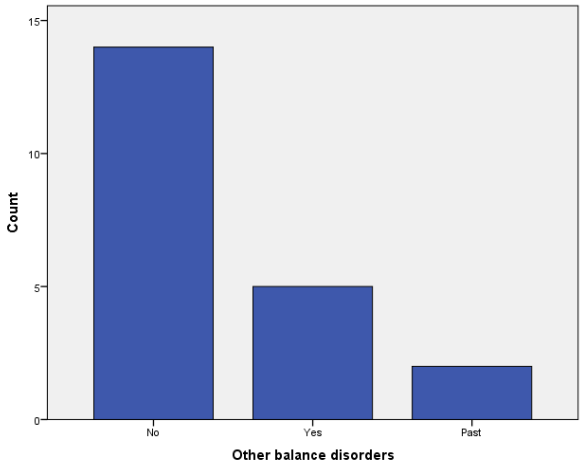

Figure 8: This bar chart represents the co-morbidity with other vestibular disorders in MdDS patients. Only 5 of the 21 patients indicated to suffer from another vestibular disorder. Additionally, one of them only suffered another vestibular disorder in the past.

3.6 Impair lifestyle

Considering the effect of MdDS on the patients' lifestyle, some external factors have been taken into account. The employment of 12 of the MdDS patients was analysed, based on the age, gender and grade on the severity-scale (Table 2).

Table 2: Representing the effect of MdDS on the patients' employment.

p – value	Age	Gender	Severity-scale
Employment	$p = 0.818$	$p = 0.014$	$p = 0.699$

Based on the age and the grade on the severity scale, there could not have been found a significant difference considering employment. But the analysis of employment based on gender, showed a significant difference between male and female patients. In this study population, there are more female than male patients who stopped working as a result of suffering from this condition (Figure 9).

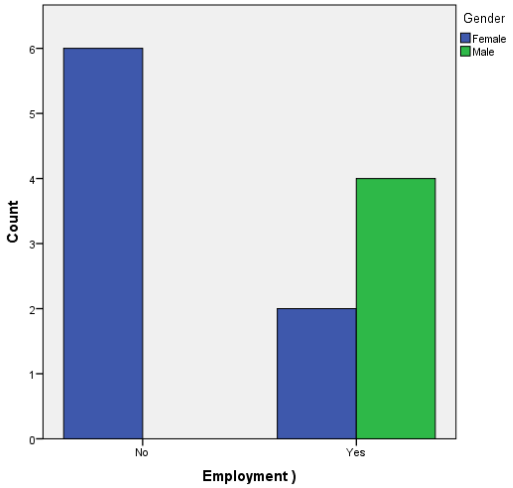

Figure 9: This bar chart represents the effect of MdDS on the patients' employment. In this study population, more female than male subjects are suffering from this condition.

Furthermore, the amount of patients taking antidepressants was considered (Table 3). Also, taking medication during the motion event has been taken into account. The analysis has been conducted based on the prevalence of taking this medication, age and gender of the patients. The evaluation of the current use of antidepressants was conducted including all patients. Considering taking antidepressants in the past, was based on 12 of the patients who filled in an extra questionnaire [5].

Table 3: Representing the effect of taking antidepressants.

p – value	Prevalence	Age	Gender
Antidepressants now	$p = 0.016$	$p = 0.075$	$p = 0.627$
Antidepressants past	$p = 0.083$	$p = 0.600$	$p = 0.157$

[5] Reference to appendix

When analysing the patients that indicated current use of antidepressants, there has been found a significant difference. Namely, only 5 of the 21 patients were taking antidepressants when completing the survey. When investigating taking antidepressants in the past, no significant difference could be obtained.

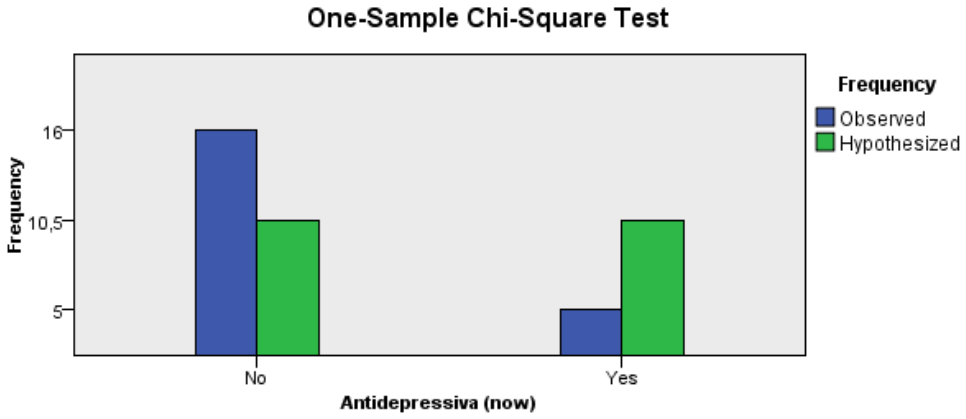

Figure 10: Bar chart of the amount of subjects taking antidepressants in the study population. The hypothesised number of subjects, differentiating on the current use of antidepressants, was compared to the observed amount of subjects.

When considering age and gender, no significant difference was obtained both in the present and in the past. Furthermore, also taking medication while travelling was taken into account. Looking for the effect on the grade on the severity scale, there could not have been found a significant difference ($p = 0.152$).

Also, trouble with sleeping was analysed as one of the external factors of the condition (Table 4). The analysis was based on age, gender and onset. As a result, MdDS patients were not significant different from healthy subjects.

Table 4: Represents the amount of subjects experiencing trouble with sleeping in the study population.

p – value	Age	Gender	Onset
Trouble with sleeping	$p = 0.360$	$p = 0.306$	$p = 1.000$

When evaluating the amount of subjects eating food containing Monosodium glutamate (MSG), no statistical analysis could have been performed as none of the patients of the study sample could answer this question properly.

Furthermore, relief in passive motion has been taken into account (Table 5). The analysis was based on gender, onset, anxiety/stress and the grade on the severity scale. This analysis demonstrated a significant difference in gender and onset. Almost all of the patients were experiencing relief in passive motion, except two of them.

These two patients were both men and indicated a spontaneous onset of the condition. Based on anxiety/stress and the grade on the severity scale, no significant difference could have been found.

Table 5: Represents the amount of subjects experiencing relief in passive motion.

p – value	Gender	Onset	Anxiety/stress	Severity scale
Relief in passive motion	$p = 0.023$	$p = 0.023$	$p = 0.264$	$p = 0.379$

3.7 Treatment outcome

The treatment was conducted in 11 of the 21 patients. For evaluating the difference in VAS-score before and after the treatment, the Wilcoxon matched-pairs signed-ranks-test was used. According to this test, a significant difference in VAS-score was obtained ($p = 0.024$). Only 4 of the 11 patients indicated not to experience any improvement of the symptoms, the other 7 experienced a small or completely relief of symptoms after being treated (Figure 13).

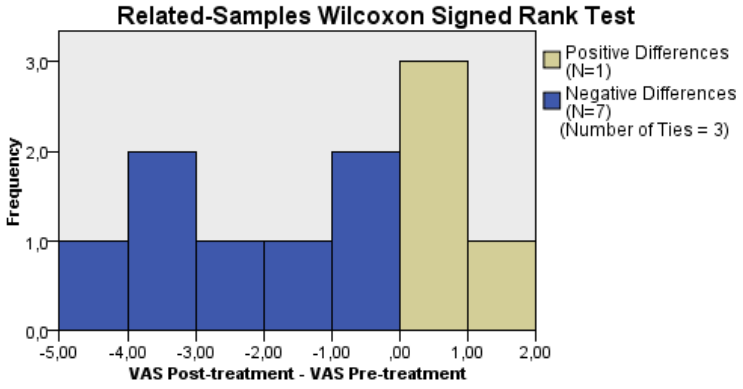

Figure 13: This bar charts represent the significant difference in VAS before and after the treatment.

Considering the treatment outcome, a statistical analysis was performed based on the duration of the symptoms, the onset, the grade on the severity scale, ΔVAS, experiencing anxiety/stress and relief in passive motion (Table 6).

In all of these variables, no significant difference in treatment outcome could have been found, except for ΔVAS. ΔVAS represents the difference in VAS-score before and after the treatment. The greater the improvement on the VAS, the better the treatment outcome was.

Table 6: Represents the treatment outcome of the study population.

p – value	Duration symptoms	Onset	Severity Scale	ΔVAS	Anxiety/stress	Relief in passive motion
Treatment outcome	$p = 0.183$	$p = 0.819$	$p = 0.497$	$p = 0.006$	$p = 0.658$	$p = 0.658$

3.8 Triggers

Evaluating the different triggers of the symptoms mentioned by the patients, the analysis was based on gender and the onset of the condition. Considering gender distribution, no significant differences could have been found for the different triggers. When evaluating the onset of the condition, there was no significant difference for the triggers, except for stress. Stress would mainly trigger patients with a motion triggered onset of the condition.

Table 7: Represents the triggers of the symptoms.

p – value	Gender	Onset
Computer	$p = 0.407$	$p = 0.890$
Stress	$p = 0.577$	$p = 0.012$
Weather	$p = 0.445$	$p = 0.760$
Caffeine	$p = 0.237$	$p = 0.844$
Laying down, standing in line	$p = 0.760$	$p = 0.445$
Busy day/long trip	$p = 0.760$	$p = 0.445$
Lack of sleep	$p = 0.627$	$p = 0.105$
Crowdy places	$p = 1.0$	$p = 0.306$
Strong emotions	$p = 0.517$	$p = 0.517$

4 Discussion

4.1 Footprint of MdDS

The aim of this study was to identify the footprint of the Mal de Debarquement Syndrome by considering epidemiological factors such as age, gender, onsets, co-morbidity and some external influences. While analysing the different features of MdDS, there were 8 components of interest.

Firstly, the results of this current study showed that the majority of the subjects were female, namely more than half of the participants were women. This is in line with the knowledge obtained from previous studies in which this female preponderance has been described before (Clark et al., 2013). In the previous literature, it has been noticed that the onset of symptoms typically occurs at the age of 40-50 years old (Cha Y. H., 2015). Considering the distribution of age in this study sample, the mean age of MdDS patients is 46.8. This value would fit in the results obtained in previous studies. However, in this study sample, no significant difference in age could have been found. The results showed that the categories [30-39], [40-49] and [50-59] most often occur in this study population.

Secondly, the experience of symptoms was evaluated. Taking into account the small study size, this research assumes that patients with MdDS experience a constant feeling of symptoms with a fluctuation when being exposed to certain triggers. The patients indicated a wide range of symptoms. Almost all of the subjects described a constant feeling of rocking, swaying and/or bobbing with a sensation of movement while standing or laying still. A greater number of MdDS patients experiences head pressure and nausea, other symptoms reported were; fatigue, balance disturbance and disorientation. Also, a minor percentage of the patients indicated memory issues, visual disturbance and light sensitivity as representing symptoms. These symptoms match with the list of symptoms which has been described in the review paper of Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts (2015).

Thirdly, the onset of this condition has been taken into account. In the existing literature, MdDS is considered to be a rare disorder due to exposure to passive motion (Dai M., Cohen, Smouha & Cho, 2014). However, in the study by Dai, Cohen, Smouha & Cho (2014), it has been mentioned that the symptoms can also occur spontaneously.

This study considered the MdDS onset in 21 subjects and, as described in the result, there were more MdDS patients reporting a motion triggered onset compared to a spontaneous onset. Namely, only 6 patients described a spontaneous onset, while the 15 others experienced a motion triggered onset of the condition.

In a research by Cha (2009), it has been described that air and land travel are possible triggers to start the condition, but sea travel has been considered to be the most prevalent trigger. When distinguishing the kind of motion event, no significant difference could have been found between air and sea travel. As a result, this research assumes that there is no remarkable difference in the kind of motion event concerning the development of MdDS.

In the previous literature, it has been described before that MdDS can have a duration from 3 days up to several years (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008; Brown & Baloh, 1987). In a research by Hain, Hanna & Rheinberger (1999), it has been mentioned that MdDS probably has a mean duration of 3.5 years, with a standard deviation of 2.5 years. Evaluating the duration of symptoms, the study population indicated a mean duration of 59.45 months (ca. 5 years) with a standard deviation of 57.32. (ca. 4.5 - 5 years). This current results appear to differ from the results of the study by Hain, Hanna & Rheinberger (1999). Looking at the distribution of duration of symptoms, most of the patients are suffering from this condition for [0-25] months (0-2 years). One patient has been suffering from MdDS since 211 months (ca. 17.5 years). As there were only 20 patients involved in this analysis, which makes it a small study population, the mean value was strongly influenced.

Fourthly, this study aimed to gather some more information concerning the possible presence of a hormonal component in the development of MdDS. In a research by Hain, Hanna & Rheinberger (1999), it has been described that the majority of the female individuals were either premenopausal or receiving hormone replacement therapy. However, considering the stage of menopause in the female patients of this study population, the results showed that the majority of the female patients didn’t reach the menopause yet. In this study, only one of the female patients indicated to be premenopausal.

Furthermore, the menstrual cycle during the motion event has been taken into account. In the study by Hain T. C. (2017), it has been illustrated that many female patients developed MdDS when being exposed to motion during their menstrual cycle. As the analysis in this current research could only be performed with the female patients who presumed the onset of the condition to be motion triggered, the group of patients only existed of 11 subjects, what makes it a small study population. However, despite the small study number, the findings were different from previous observations as only 1 of the patients indicated having her menstrual cycle during the motion event.

As a result, considering the small study population, the current research concluded that the menstrual cycle has no specific influence on the development of MdDS in this specific group of patients. Moreover, this study considered whether the patients were taking any contraceptive at the moment of the onset, but no significant findings were observed. As a result, the hormonal component in female MdDS patients appears not to have an effect on the development of the condition. Further investigations are needed to evaluate this aspect more closely.

Another important aspect, which we would like to introduce as the fifth component of interest, is the co-morbidity of MdDS with other (vestibular) disorders. The existing literature assumed that MdDS patients have a higher prevalence of migraine than the population prevalence, especially MdDS patients who experienced a spontaneous onset of the condition (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). Evaluating the co-morbidity of MdDS with migraine, the prevalence of migraine in the population was considered to be 22% in female subjects, based on a study by Rasmussen, Jensen, Schroll & Olesen (1991).

The co-morbidity with migraine was only analysed in the female patients, as previous studies assumed that there is a female predominance for the co-morbidity of MdDS with migraine (Clark et al., 2013). This current research concluded that there was no significant difference in the prevalence of migraine in the study sample compared to the standard population. Also, the distribution of gender and age was taken into account, however no significant difference could have been found. Previous studies assumed that there could be a preponderance for patients who indicated spontaneous onset of the disease (Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008).

Considering the co-morbidity of MdDS with migraine based on the onset of the condition, this current research didn't find a remarkable difference. Taking in mind the small amount of subjects, this research assumes that there is not a significant prevalence of migraine in patients suffering from MdDS.

Furthermore, the relation of MdDS with motion sickness has been taken into account. Several studies recognised potential links between MdDS and motion sickness (Tal, Wiener & Shupak, 2014; Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008; Kurre, Straumann, Van Gool, Gloor-Juzi & Bastiaenen, 2012; Murphy, 1993). Evaluating the co-morbidity of MdDS with motion sickness in this study sample, the population prevalence of motion sickness was considered to be 28% based on the investigation by Sharma (1997). In this current research, no significant difference could have been found in the prevalence of motion sickness in the study sample compared to the standard population. The age, gender and the onset of the disease also have been taken into account. As a result, this study presumes that there is no significant prevalence of motion sickness in patients with MdDS.

In the research by Cha Y. H.(2015), it has been mentioned that individuals with MdDS spend significant time, energy and money trying to be diagnosed and treated, as a result high levels of depression and anxiety are often observed in MdDS patients, which can lead to a poor quality of life (Clark et al., 2013). Taking into account this previous studies, this current research aimed to evaluate the co-morbidity of MdDS with depression and anxiety. The prevalence of depression in the population was considered to be 8.5 %. This quantity was based on the results obtained in the study by Aysuso-Mateos et al. (2001). When analysing the co-morbidity of MdDS with depression and anxiety based on gender, age and the onset of the disease, no significant results were obtained. As a result, this current study assumes that there is no remarkable difference in the prevalence of depression in patients suffering from MdDS comparing the standard population.

Also, this research considered the amount of patients taking antidepressants before and after the onset of the symptoms. When evaluating the patients that indicated current use of antidepressants, this study concluded that most MdDS patients are not taking any antidepressants as a result of suffering from this condition.

Analysing the use of antidepressants in the past, no significant difference could have been found. Moreover, according to this assessment, taking medication during the motion event has no effect on the grade of symptoms on the severity-scale.

Thus, the co-morbidty with tinnitus has been analysed. In the existing literature it has been noticed that some of the MdDS patients are also affected by tinnitus (Van Ombergen, Van Rompaey, Maes, Van de Heyning & Wuyts, 2015; Cha, Brodsky, Ishiyama, Sabatti & Baloh, 2008). The prevalence of tinnitus in the population was considered to be 15%, this quantity was based on the results of the investigation by Hoffman & Reed (2004). Considering the difference in prevalence comparing the standard population, a significant part of the study population has tinnitus too. This information is in line with the previous knowledge. Further research is needed, therefore the underlying pathogenesis of both entities should be further investigated first.

Sixth, the effect of the condition on the patients' lifestyle has also been evaluated. As MdDS is considered a rare condition and as it is often undiagnosed or misdiagnosed, it has been noticed in previous studies that the condition has a big socio-economic impact (Clark et al., 2013). In those previous studies, it was observed that a lot of patients suffering from MdDS needed to quit their job. As a result, the employment of 12 of the MdDS patients was considered with their age, gender and severity of symptoms (severity scale). The amount of people that quit their job due to suffering from MdDS, appeared to be equal to the amount of subjects that are still working. Evaluating the employment based on gender, taking into account the small sample of patients, more female then male patients appeared to quit their job. Further investigation is needed to reconfirm this statement with a larger study population.

In previous studies, it has also been described that MdDS can have severe effects on the patients' lifestyle (Clark et al., 2013). To objectify this, patients were asked about their sleeping routines and patters. As a result, taking into account the small study population, this current research assumes that the condition has no significant effect on the patients' sleep.

In the study by Cha Y. H. (2015) it has been noticed that, regardless the onset of the condition, patients suffering from MdDS are often experiencing a remission of symptoms when being (re)-exposed to passive motion.

The results of this study were in line with previous assessments, as 19 of the patients of this study population are experiencing relief of symptoms when being (re)-exposed to passive motion. Most of them reported to be relieved from the constant sensation of rocking, bobbing and swaying when being riding in a car. When evaluating gender and onset of the symptoms, this research assumes that there is a remarkable difference. However, only 2 of the patients didn't experience relief in passive motion. These two patients were both men and indicated a spontaneous onset of the condition. Taking into account the small sample of subjects, this current study presumes careful that more female patients experience relief of symptoms. Also, when the onset of the condition is motion triggered, more patients will indicate a remarkable relief after exposure to passive motion. As this current research contains a small sample of study subjects, this findings should be reconfirmed by further investigations.

The seventh point of assessment was considering the VOR treatment, based on the VOR re-adaptation (Dai M., Cohen, Smouha & Cho, 2014). The VAS-score before and after the treatment was compared. Once again, although the small number of subjects, the VOR protocol appeared to be beneficial as the severity of the symptoms decreased. Also, it has been observed that the treatment outcome is not influenced by the duration of the symptoms or by the onset of the condition. The outcome was independent from the severity of MdDS, associated anxiety/stress and relief in passive motion as well.

Lastly, this study showed that all of the multiple triggers, able to affect MdDS, were equal for male and female patients. Looking at the onset of the condition, stress has been observed to mainly trigger patients with a motion triggered onset.

While discussing all of this features, it is important that the small study size has been taken into account. Further research should provide more evidence into the exact underlying mechanism of this condition. By investigating the most common aspects, it may be possible to understand the cause of Mal de Debarquement Sydrome and to lead for the development of a successful treatment .

4.2 Limitations and future research

As the recruitment of patients happened in a short period of time, the study population appeared not to be sufficient comparing other epidemiological investigations concerning the Mal de Debarquement Syndrome. Therefore, we acknowledge the limitation of having a small number of subjects and we would like to consider this current investigation as a first pilot-study.

For some features, only the 11 subjects treated and recruited in Antwerp University Hospital (UZA, Belgium) were considered as this study achieved more information about the clinical and social history of this patients. We expect that when some of the patients are experiencing a positive outcome, more patients will hear from it through the social media and the aimed group of 30 could be attained in a following study. As this research assumes some contradictory results compared to other investigations with a larger cohort, it seems logical to re-conduct this research with a larger study sample so that we can assure that the predetermined conclusions were fully correct.

5 Conclusion

In conclusion, the online questionnaires have shown to be able to provide us information, however it would be ideal to gather a larger number of patients who received the diagnosis of the condition by the same doctor. Also, once the treatment procedure is further investigated, a new study should be set-up to assess the best treatment methods, as this was not fully determined yet. Furthermore, we take into account the limitation of the VOR protocol, which has not yet included a control study.

The co-morbidity with other disorders has been investigated based on existing epidemiological studies. As previously described no significant difference was noted for motion sickness, migraine and depression. However, the main prevalence of MdDS patients suffering from tinnitus was significant higher than in the general population. Given those preliminary findings, we encourage the research to continue in order to understand the pathophysiology of MdDS.

6 References

Andrews, J. C., Ator, G. A. & Honrubia, V. (1992). Exacerbations of symptoms in Meniere's disease during the premenstrual period. *Achieves of otolaryngology-head and neck surgery*, 118(1): 74-78.

Arroll, M., Attree, E., Cha, Y. & Dancey, C. (2014). The relationship between symptom severity, stigma, illness intrusiveness and depression in Mal de Debarquement Syndrome. *Journal of Health Psychology*. doi:10.1177/1359105314553046

Aysuso-Mateos, J.L., Vasquez-Barquero, J. L., Dowrick, C., Lehtinen, V., Dalgard, O. S., Casey, P., Wilkinson, C., Lasa, L., Page, H., Dunn, G. & Wilkinson, G. (2001). Depressive disorders in Europe: prevalence figures from the ODIN study. *British Journal of Psychiatry*, (179) 308-316.

Brown, J. & Baloh, R. (1987). Persistent mal de debarquement syndrome: a motion-induced subjective disorder of balance. *Am. J. Otolaryngol*, 219-222.

Cha, Y. H. (2009). Mal de debarquement. *Semin Neurol* , 29(5): 520-527.

Cha, Y. H. (2015). Mal de debarquement syndrome: new insights. *Ann. N.Y. Acad. Sci.*, 63-68.

Cha, Y. H. & Chakrapani, S. (2015). Voxel Based Morphometry Alterations in Mal de Debarquement Syndrome. *PLoS ONE 10(8)*, e0135021. doi:10.1371/journal.pone.0135021.

Cha, Y. H., Brodsky, J., Ishiyama, G., Sabatti, C. & Baloh, R. (2008). Clinical features and associated syndromes of mal de Debarquement. *J Neurol.*, 255(7): 1038.

Cha, Y. H., Chakrapani, S., Craig, A. & Baloh, R. (2012). Metabolic and Functional Connectivity Changes in Mal de Debarquement Syndrome. *PLoS ONE 7*, e49560., doi:10.1371/journal.pone.0049560.

Cha, Y. H., Cui, Y. & Baloh, R. (2013). Repetitive transcranial magnetic stimulation for Mal de Debarquement Syndrome. *Otol Neurotol*, 34(1), 175–179.

Cha, Y. H., Urbana, D. & Pariseau, N. (2016). Randomized Single Blind Sham Controlled Trial of Adjunctive Home-Based tDCS after rTMS for Mal De Debarquement Syndrome: Safety, Efficacy, and Participant Satisfaction Assessment. *Brain Stimulation 9*, 537–544.

Cha, Y. & Cui, Y. (2013). Rocking dizziness and headache: a two-way street. *Cephalalgie*, 1160-1169.

Clark, B. & Quick, A. (2011). Exploring the pathophysiology of Mal de Debarquement. . *J Neurol*, 258, 1166–1168.

Clark, B., LePorte, A., Clark, S., Hoffman, R., Quick, A., Wilson, T. & Thomas, J. (2013). Effects of persistent Mal de debarquement syndrome on balance, psychological traits and motor cortex excitability. *Journal Of Clinical Neuroscience 20*, 446-450.

Dai, M., Cohen, B., Cho, C., Shin, S. & Yakushin, S. B. (2017). Treatment of the Mal de Debarquement Syndrome: A 1-Year Follow-up. *Neurol.*

Dai, M., Cohen, B., Smouha, E. & Cho, C. (2014). Readaptation of the vestibulo-ocular reflex relieves the mal de debarquement syndrome. *Frontiers and neurology*, doi: 10.3389/fneur.2014.00124.

Deschepper, E., Buysse, H. & Coorevits, P. (2016). *Statistische Gegevensverwerking met behulp van IBM SPSS Statistics 23.* Gent: University Press Gent.

Ghavami, Y., Haidor, Y. M., Ziai, K. N., Moshtaghi, O., Bhatt, J., Lin, H. W. & Djalilian, H. R. (2016). Management of mal de debarquement syndrome as vestibular migraines. *Laryngoscope*, doi: 10.1002/lary.26299.

Gordon, C., Spitzer, O., Doweck, I., Melamed, Y. & Shupak, A. (1995). Clinical features of mal de debarquement: adaptation and habituation to sea conditions. *J. Vestib. Res.*, 5(5):363-369.

Hain, T. C. (2017, February 22). *Mal de Debarquement Syndrome (MdDS or MdDS)*. Opgehaald van Dizziness and balance: http://www.dizziness-and-balance.com/disorders/central/mdd.html

Hain, T. C., Hanna, P. A. & Rheinberger, M. A. (1999). Mal de Debarquement. *Arch Otolaryngol Head Neck Surg*, 125: 615-620.

Hoffman, H. J. & Reed, G. W. (2004). Epidemiology of tinnitus. In *Tinnitus Theory and management* (pp. 16-41). Lewiston, NY: BC Decker Inc.

Kurre, A., Straumann, D., Van Gool, C., Gloor-Juzi, T. & Bastiaenen, C. (2012). Gender differences in patients with dizziness and unsteadiness regarding self-perceived disability , emotional distress , symptom severity and its associations. *BMC Ear Nose Throat Disord*, 12(2):1-23.

MacKe, A., LePorte, A. & Clarck, B. C. (2012). Social, societal, and economic burden of mal de debarquement syndrome. *J Neurol* , 259(7):1326–1330.

Mauskop, A. (2012, april 16). *Mal de Debarquement Syndrome*. Opgehaald van New York Headache blog: http://www.nyheadache.com/blog/

Murphy, T. P. (1993). Mal de debarquement syndrome: a forgotten entity? *Otolaryngol Head Neck Surg.*, 109(1): 10-13.

Pearce, A., Davies, C. & Major, B. (2015). Efficacy of neurostimulation to treat symptoms of Mal de Debarquement Syndrome: a preliminary study using repetitive transcranial magnetic stimulation. *Journal of Neuropsychology 9*, 336–341.

Rasmussen, B. K., Jensen, R., Schroll, M. & Olesen, J. (1991). Epidemiology of Headache in a general population: a prevalence study. *J. Clin. Epidemiol.*, 44(11): 1147-1157.

Saltsman, K. (2014). Finding Steady Ground: Insight Into the Cause of Severe Balance Disorder Brings Promising Therapeutic Approach. *Inside NIDCD Newsletter*.

Sharma, K. (1997). Prevalence and Correlates of Susceptibility to Motion Sickness. *Acta Genet Med Gemellol (Roma).*, 46(2): 104-121.

Sharon, J. D. & Hullar, T. E. (2014). "Motion sensitivity and caloric responsiveness in vestibular migraine and Meniere's disease." *Laryngoscope*, 124(4): 969-973.

Tal, D., Wiener, G. & Shupak, A. (2014). Mal de debarquement, motion sickness and the effect of an artificial horizon. *J. Vestib. Res.*, 24(1): 17-23.

Talarska, D., Zgorzalewicz-Stachowiak, M., Michalak, M., Czajkowska, A. & Hudaś, K. (2014). Functioning of Women with Migraine Headaches. *The Scientific World Journal*.

Van Ombergen, A., Van Rompaey, V., Maes, L., Van de Heyning, P. & Wuyts, F. (2015). Mal de debarquement syndrome: a systematic review. *J Neurol*, DOI 10.1007/s00415-015-7962-6.

Van Ombergen, A., Wuyts, F. & Cha, Y. H. (2016). Letter to the Editor: comment and erratum to "Mal de debarquement syndrome: a systematic review". *J Neurol*, Doi 10.1007/s00415-016-8102-7.

Wiseman, V. (2005). Using diaries to collect data resource-poor settings: questions on design and implementation. *Health Policy and planning*, 20(6): 394-404.

Xiong, J. S., Branigan, D. & Li, M. (2009). Deciphering the MSG controversy. *International Journal of Clinical and Experimental Medicine*, 2(4), 329-336.

Zigmond, A. S. & Snait, Z. (1883). The hospital anxiety and depression scale. . *Acta Psychiatr. Scand.*, 67(6): 361-370.

7 Appendix

7.1 Patient information sheet and informed consent questionnaire (English)

PATIENT INFORMATION SHEET

You are invited to participate voluntarily in a clinical study. Before you participate in this study, it is important that you read this form and complete the questionnaire and consent form. This sheet explains the purpose of the investigation, the benefits, the risks and inconveniences associated with the described study. You have the right to leave the study at any time. No promises can be made or warranties given concerning the results of the study. Investigations linked to the study and the experimental treatment will not be charged. You have the right to ask questions at any time via the contact details provided at the end of these documents.

Background: Mal de Debarquement Syndrome (MdDS) is a condition characterized by a subjective sensation of self-motion (rocking, swaying and bobbing), which persists after initial exposure to passive movement, usually after a journey by sea, but sometimes after air travel or overland. Mal de Debarquement (MdD) symptoms are often reported and they are quiet a common phenomenon in people exposed to passive motion, however they usually resolve with less than 48 hours. Nevertheless, some people do not recover from the symptoms and the complaints often last for months or years after the initial exposure to passive motion. In this case we talk of Mal de Debarquement Syndrome (MdDS), which is a pathological condition and is accompanied by a considerable psycho-social and economic impact. MdDS is considered to be a rather rare condition of which the underlying mechanisms are still unclear.

It has been described before that the majority of the MdDS patients are females. It is known that hormones play an important role in various vestibular pathologies such as vestibular migraine, and Meniere's disease.

With the following intake form, we aim to gain data regarding MdDS patients and to understand more about their symptoms and triggers. Additionally, with the electronic diary, we aim to track symptoms aggravation due to multiple triggers and in female subjects due to their hormonal fluctuations within the menstrual cycle. As a result, the current research is mostly directed to women suffering MdDS. If men are willing to participate please exclude the questions related to women.

Your identity and your participation in this study will be kept strictly confidential. In accordance with the Belgian law of December 8, 1992 and the Belgian law of August 22, 2002, your privacy will be respected. You will not be identified by name, or in any other manner in files, results or publications related to the study. The researchers will encrypt your personal information, this means they will be using a code which can lead back to the personal file of the participant, the data will be anonymised. The investigation will satisfy the requirements according to the Belgian Law of May 7, 2004, concerning experiments on the human person.

There are no risks associated with the current study. Your participation will benefit the Research Center for Equlibrium and Aerospace (AUREA) from Antwerpen University to have more data available for further research. No compensation is currently available.

If you experience any damage resulting from your participation in the study, you or your beneficiaries will be reimbursed by the sponsor of this study for the damage, in accordance with the Belgian Law of May 7, 2004, concerning experiments on the human person

You won't need to demonstrate any error. The client has taken out a civil liability insurance risks and the damage that would result from this study cover. You or your beneficiaries can sue the insurer directly at any time in Belgium.

We greatly appreciate your time and the information you provide in this study. We acknowledge that using computers is not easy for people with MdDS and can exacerbate symptom levels. Please take regular breaks when using your computer to complete these forms.

Please do not disclose this diary and the information form with other research group without consulting us.

CONSENT FORM: To participate to the Mal de Debarquement Syndrome research

Part only for the patient or legal representative:

- ✓ I ……acknowledge the undersigned form page 1-3. I am informed of the study and a copy of the Patient Information Sheet and Consent Form were received. I have read and understood the information.
- ✓ I understand that I may discontinue my participation in this study at any time after I informed my doctor about it, without this causing me any harm. (N.B. Informing your doctor about your participation in this study is voluntary.)
- ✓ I give permission to the leaders of the sponsor and regulatory authorities to have access to the medical information provided via this study. My medical information will be kept strictly confidential. I am aware of the purpose for which such data is processed and used in the context of this study.
- ✓ I agree to the collection, processing and use of this medical data, as described in the information sheet for the patient. I also agree to the transfer and processing of such data in countries other than Belgium.
- ✓ I agree to the use by the client of this encrypted medical data for other research purposes.
- ✓ I agree completely voluntarily to participate in this study and to participate in any kind of investigation. I am willing to provide information about my medical history, my drug use and eventual participation in other studies.
- ✓ I agree that my doctor / specialist and other health care providers involved in my treatment may be informed of my participation in this study, if necessary.

Name & Surname **Signature** **Date (day.month.year)**

…… ……. …….

If you complete this form electronically you can use an electronic signature or simply type your name again where indicated.

Part only for the research team:

I .....confirm that his / her legal representative have been informed and that he - she has given permission to participate in the study.

Name & Surname **Signature** **Date (day.month.year)**

…….. ……..... ……..

7.2 Patient information sheet and informed consent treatment (Dutch)

Studie: Behandeling van Mal de Debarquement Syndroom door middel van readaptatie van de Vestibulo Oculaire Reflex

PATIENTENINFORMATIE

U wordt uitgenodigd om vrijwillig deel te nemen aan een klinische studie. Vooraleer u toestemt om aan deze studie deel te nemen, is het belangrijk dat u dit formulier leest. In dit informatie- en toestemmingsformulier worden het doel, de onderzoeken, de voordelen, risico's en ongemakken, gepaard gaande met de studie, beschreven. Er wordt ook beschreven dat u het recht heeft om op elk ogenblik de studie te verlaten. Er kunnen geen beloften gedaan worden noch waarborgen gegeven worden betreffende de resultaten van de studie. Onderzoeken, verbonden aan de studie en/of de experimentele behandeling, zullen niet in rekening worden gebracht. U heeft het recht om op elk ogenblik vragen te stellen over de mogelijke en/of bekende risico's die deze studie inhoudt.

Achtergrond

Mal de Debarquement is een conditie gekarakteriseerd door een subjectieve sensatie van zelfbeweging (wiegen, schommelen, zwaaien of dobberen) die aanhoudt na initiële blootstelling aan passieve beweging, meestal na een reis over zee, maar soms ook na vliegreizen of overlandse reizen. Kortstondige Mal de Debarquement klachten (<48u) zijn een vaakvoorkomend fenomeen. Sommige mensen recupereren echter niet en blijven aanhoudende klachten van mal de debarquement behouden gedurende maanden tot jaren na de initiële blootstelling aan passieve beweging. In dit geval spreekt men van het Mal de Debarquement Syndroom (MdDS) , hetgeen wel een pathologische conditie is en gepaard gaat met een aanzienlijke psychosociale en economische impact. Het is een eerder zeldzame aandoening waarvan het onderliggende mechanisme tot op heden onduidelijk is, waardoor er maar beperkte behandelingsmogelijkheden zijn.

Recent is een studie gepubliceerd waarbij men poogde om de klachten te verminderen door een full-field optokinetische stimulus aan te bieden bij gelijktijdige hoofdrolbeweging. (Dai M, Cohen B. Readaptation of the vestibule-ocular reflex relieves mal de debarquement syndrome, Front Neurol, 2014) De resultaten van de voorgenoemde studie zijn veelbelovend met een verbetering van de klachten in 70% van de studiepatiënten.

Er is nood aan voldoende visuele informatie om een goede perceptie van het lichaam in de omgeving te verkrijgen, dit probeert men te verkrijgen aan de hand van een optokinetishe stimulus. Indien een patiënt onophoudelijk kijkt naar een scherm met een visuele stimulus die het gezichtsveld volledig vult en naar links draait, dan zal die patiënt het gevoel hebben dat zijn of haar lichaam naar de tegenovergestelde zijde (rechts) roteert. De patiënt zal zich dan reoriënteren naar links, in een poging om deze rotatie te compenseren.

Doel van de studie

Het doel van deze studie is na te gaan of bovenstaande resultaten reproduceerbaar zijn en te onderzoeken of de klachten bij patiënten met Mal de Debarquement Syndroom (MdDS) verminderd kunnen worden door middel van het aanbieden van bewegende doorgaans verticale strepen (optokinetische stimulus) waarbij gelijktijdig met het hoofd een rolbeweging gemaakt wordt.

Beschrijving van de studie

De initiële rekrutering van de studiepatiënten gebeurt via de vertigo-raadpleging op de dienst NKO van het universitair ziekenhuis Antwerpen. Hier zal de standaard uitwerking voor een patiënt met vertigo plaatsvinden, inclusief de daarbij horende onderzoeken. Er zal initieel een uitgebreide anamnese gebeuren, een klinisch onderzoek met micro-otoscopie (kijken naar de trommelvliezen met behulp van vergroting door de microscoop) en video-oculoscopie (door middel van een videobril de oogbewegingen/nystagmus bestuderen die informatie geven over het evenwichtssysteem), gehoortesten (tonale audiometrie, spraakaudiometrie en tympanometrie), een magnetische resonantie scan van het hoofd en de brughoek regio waarin het perifeer evenwichtsorgaan zich begeeft, en een aanvullend evenwichtsonderzoek aan de hand van elektronystagmografie (evenwichtsonderzoek waarbij oogbewegingen elektrisch worden geregistreerd) en/of vestibulair geëvokeerde myogene potentialen (ipsilaterale inhiberende spierpotentialen kunnen worden opgemeten ter hoogte van de sternocleidomastoideus spier. Deze potentialen worden uitgelokt door luide akoestische stimulaties (clicks of tone bursts)).

Indien u na deze op puntstelling voldoet aan de inclusiecriteria van MdDS voor onze studie, zal u gevraagd worden deel te nemen en zal de gehele studieprocedure mondeling overlopen worden. U krijgt de tijd om na te denken om te beslissen al dan niet deel te nemen. Indien u beslist deel te nemen, dient u het informed consent te tekenen.

De studie bestaat uit deelname aan een experimentele behandeling voor MdDS waarbij er gepoogd wordt de klachten te reduceren door de patiënt de stimuleren met een visueel optokinetische stimulus, met name een strepenpatroon dat beweegt met een bepaalde snelheid (5 tot 10°/sec) in een bepaalde richting (links-rechts-boven-onder).

U zal gedurende de behandeling neerzitten op een stoel in een verduisterde ruimte. U dient gedurende de behandeling de ogen open te houden terwijl gelijktijdig de onderzoeker uw hoofd zal bewegen volgens een bepaalde frequentie (0,01-0,7Hz).

Bovendien, vrouwelijke proefpersonen rapporteren vaak een verergering van de symptomen, waarschijnlijk als gevolg van hormonale schommelingen. Deze vrouwen zullen gevraagd worden om deel te nemen aan het hormonale onderzoek, indien zij geen anticonceptie nemen. Meer specifiek, zullen zij gevraagd worden om hun symptomen en fluctuaties hiervan bij te houden in een dagboek en twee bloedafnames te ondergaan in een specifieke tijd van hun menstruele cyclus.

Voorafgaand en na iedere sessie zullen een aantal balanstesten gebeuren en dienen enkele vragenlijsten ingevuld te worden:

Posturografie met Nintendo Wii© Balance bord

Hierbij zal u gevraagd worden om rechtop gedurende 1 minuut met gesloten ogen en beide voeten tegeneen op een Wii- balans bord te gaan staan. Dit geeft informatie over uw posturale balans.

3D-accelerometer thv de pols van Xsens©

Hierbij wordt u gevraagd de frequentie van de intern waargenomen bewegingen (wiegen, schommelen) aan te geven met uw pols. Er zal hiervoor een polsband met een snelheidsmeter gebruikt worden. U dient uw pols te bewegen volgens de frequentie van de beweging die u ervaart terwijl uw elleboog rust op de tafel en u uw ogen sluit gedurende 30 seconden.

Fukada stepping-test

Hierbij zal u gevraagd worden om ter plaatste te stappen gedurende 1 minuut, met gesloten ogen en armen vooruit gestrekt. Deze test geeft opnieuw informatie over uw posturale balans.

Vragenlijsten

U zal een aantal vragenlijsten moeten invullen waarbij gepeild wordt naar onder andere uw evenwichtslast, de geassocieerde misselijkheid en de weerslag en gevolgen ervan. Het betreft de volgende vragenlijsten: Misery Scale (MISC), Visueel Analoge Schaal-score(VAS-score), BRUM stemming vragenlijst.

Daarnaast zullen de vrouwelijke studie-patiënten vriendelijk verzocht worden een patiëntendagboek ter registratie van de klachten en geassocieerde symptomen dagelijks in te vullen. Dit te starten vanaf minimum één maand voor de behandeling aanvangt en te continueren tot minimum één maand na einde van behandeling. Het dagboek dient steeds ingevuld te worden op het zelfde moment van de dag, bij voorkeur ’s avonds.

Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan dit ziekenhuis, en zal worden uitgevoerd volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki opgesteld ter bescherming van mensen deelnemend aan klinische studies. Deze verzameling wordt uitgevoerd onder supervisie van Prof. Dr. Wuyts.

Duur van de klinische studie

In het totaal zal de behandeling bestaan uit 5 sessies, 1 sessie per dag gedurende 5 opeenvolgende dagen. Een sessie bestaat uit zowel de balanstesten, vragenlijsten, als de eigenlijke behandeling met optokinetische stimulus. Iedere sessie zal ongeveer 45minuten in beslag nemen.

Vrijwillige deelname

U neemt geheel vrijwillig deel aan deze studie en u heeft het recht te weigeren er aan deel te nemen. Uw beslissing om al dan niet aan deze studie deel te nemen of om uw deelname aan de studie stop te zetten zal geen enkele invloed hebben op uw verdere behandeling.

Indien u aanvaardt om deel te nemen aan de studie, dient u deze informatiefolder te bewaren en zal u gevraagd worden het aangehechte toestemmingsformulier te ondertekenen.

U hebt het recht om uw deelname aan de studie op elk ogenblik stop te zetten, zelfs nadat u het toestemmingsformulier ondertekend heeft. U hoeft hiervoor geen reden te vermelden. Het intrekken van uw toestemming zal geen enkel nadeel of verlies van voordelen met zich meebrengen. Uw beslissing zal geen weerslag hebben op uw verdere medische behandeling. Uw beslissing zal ook geen weerslag hebben op uw relatie met uw behandelende arts.

Uw deelname in de studie kan ook, zonder uw toestemming, op elk ogenblik stopgezet worden door de onderzoeksarts, de Commissie voor Medische Ethiek of door de opdrachtgever. Mogelijke redenen voor zulke beslissing kunnen onder andere zijn:

• U houdt zich niet aan de instructies voor deelname aan de studie;
• uw verdere deelname aan de studie blijkt schadelijk voor u te zijn;
• er wordt tijdens de studie vastgesteld dat u toch niet aan de studievoorwaarden voldoet.

Voordelen

Wij kunnen u niet garanderen dat, indien u toestemt om aan deze klinische studie deel te nemen, u persoonlijk enig rechtstreeks voordeel zal halen uit uw deelname aan deze studie. Maar u zal bijdragen aan de huidige kennis met betrekking tot het Mal de Debarquement Syndroom.

Risico's en ongemakken

Mogelijks kan u misselijkheid, duizeligheid en/of hoofdpijn ervaren tijdens of na de onderzoeken. Deze klachten zijn echter van voorbijgaande aard.

Verzekering

Indien u schade ondervindt als gevolg van uw deelname aan de studie, zal u of uw rechthebbenden door de opdrachtgever van deze studie vergoed worden voor deze schade, overeenkomstig de geldende Belgische wetgeving. U hoeft hiervoor geen fout aan te tonen. De opdrachtgever heeft een burgerlijke aansprakelijkheidsverzekering afgesloten die de risico's en de schade, die zouden voorvloeien uit deze studie, dekken. U of uw rechthebbenden kunnen hiervoor op elk ogenblik in België de verzekeraar rechtstreeks dagvaarden. Dit zal verlopen volgens de Belgische wet van 7 mei 2004, inzake experimenten op de menselijke persoon.

Vergoeding

Er is geen vergoeding voor deze studie.

Bescherming van de persoonlijke levenssfeer

Uw identiteit en uw deelname aan deze studie worden strikt vertrouwelijk behandeld. In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal uw persoonlijke levenssfeer worden gerespecteerd. U zal niet bij naam of op een andere wijze geïdentificeerd worden in dossiers, resultaten of publicaties in verband met de studie. De onderzoekende arts zal uw persoonsgegevens coderen zodat uw identiteit altijd geheim zal blijven. Dit houdt in dat de gegevens enkel nog door middel van een code teruggekoppeld kunnen worden naar het persoonlijk dossier van de deelnemer, de gegevens zullen worden geanonimiseerd.

Overeenkomstig de richtlijnen van Goede Klinische Praktijken zal inzage in uw medisch dossier verleend worden aan vertegenwoordigers van de opdrachtgever of zijn filialen en aan de regelgevende overheden, en voor zover dit verband houdt met de studie. Dit heeft tot doel de studiegegevens en -onderzoeken na te gaan en te verzekeren dat de informatie nauwkeurig is. Uw studiegegevens worden elektronisch (d.w.z. in de computer) of handmatig verwerkt en geanalyseerd om de resultaten van deze studie te bepalen.

U heeft het recht aan de onderzoeksarts te vragen welke gegevens er over u worden verzameld in het kader van de studie en wat de bedoeling ervan is. U heeft ook het recht aan de onderzoeksarts te vragen om u inzage te verlenen in uw persoonlijke informatie en er eventueel de nodige verbeteringen in te laten aanbrengen. De bescherming van de persoonlijke gegevens is wettelijk bepaald door de geldende wet- en regelgeving betreffende de bescherming van de persoonlijke levenssfeer.

Indien u toestemt deel te nemen aan dit onderzoek betekent dit dat u toestemming geeft tot het gebruik van uw gecodeerde medische gegevens voor bovenstaande doeleinden en tot het overmaken ervan aan bovenvermelde personen en/of instanties.

Indien uw studiedeelname voortijdig gestopt wordt, zal uw initiële toestemming het gebruik toelaten van uw studiegegevens met betrekking tot de periode dat u in de studie ingesloten was.

TOESTEMMINGSFORMULIER Behandeling van Mal de Debarquement Syndroom door middel van readaptatie van de Vestibulo Oculaire Reflex

Deel enkel bestemd voor de patiënt(e) of de wettelijke vertegenwoordig(st)er:

Hierbij bevestig ik, ondergetekende …… dat ik over de studie ben ingelicht en een kopie van de "Informatie voor de Patiënt en Toestemmingsformulier" ontvangen heb. Ik heb de informatie van pagina's 1-5 gelezen en begrepen. Mijn arts heeft mij voldoende informatie gegeven met betrekking tot de voorwaarden en de duur van de studie, én het effect en de bijwerkingen van deze behandeling. Bovendien werd mij voldoende tijd gegeven om de informatie te overwegen en om vragen te stellen, waarop ik bevredigende antwoorden gekregen heb.

• Ik heb begrepen dat ik mijn deelname aan deze studie op elk ogenblik mag stopzetten nadat ik mijn arts hierover heb ingelicht, zonder dat dit mij enig nadeel kan berokkenen.

• Ik geef toestemming aan de verantwoordelijken van de opdrachtgever en aan regulerende overheden om inzage te hebben in mijn patiëntendossier. Mijn medische gegevens zullen strikt vertrouwelijk behandeld worden. Ik ben mij bewust van het doel waarvoor deze gegevens verzameld, verwerkt en gebruikt worden in het kader van deze studie.

• Ik ga akkoord met de verzameling, de verwerking en het gebruik van deze medische gegevens, zoals beschreven in het informatieblad voor de patiënt. Ik ga eveneens akkoord met de overdracht en de verwerking van deze gegevens in andere landen dan België.

• Ik ga akkoord met het gebruik door de opdrachtgever van deze gecodeerde medische gegevens voor andere onderzoeksdoeleinden.

• Ik stem geheel vrijwillig toe om deel te nemen aan deze studie en om mee te werken aan alle gevraagde onderzoeken. Ik ben bereid informatie te verstrekken i.v.m. mijn medische geschiedenis, mijn geneesmiddelengebruik en eventuele deelname aan andere studies.

• Ik ga ermee akkoord dat mijn huisarts/specialist en andere zorgverleners die bij mijn behandeling betrokken zijn, indien nodig, op de hoogte worden gebracht van mijn deelname aan dit onderzoek.

Naam	**Handtekening**	**Datum (dag/maand/jaar)**
……..	…….....	……..

Deel enkel bestemd voor het onderzoeksteam

Ik bevestig hierbij dat ik …….. of zijn/haar wettelijke vertegenwoordig(st)er) heb ingelicht en dat hij (zij) zijn (haar) toestemming heeft gegeven om deel te nemen aan de studie.

Naam	**Handtekening**	**Datum (dag/maand/jaar)**
……..	…….....	……..

7.3 Questionnaire

ON- LINE Questionnaire MdDS Research

Please complete the following questionnaire. The aim of this document is to gain information about your current health status and additional records information, which are going to be useful to our team. This questionnaire is exclusive for MdDS patients.

General information

Name:

Gender:

Age:

Ethnicity:

Address:

Phone:

Email:

When have you been diagnosed with MdDS:
Since when do you suffer from MdDS:

MdDS Symptoms related questionnaire:

1) Who diagnosed you with MdDS (Neurologist, Otolaryngologist, PT, self)?

2) Do you suffer from any additional pathological conditions or are you under any specific medication we should be aware of? *(If under contraceptive please specify the type and duration)*

3) To your best knowledge, what was the motion event that induced MdDS (e.g., cruising, boating, air flight, train)? *(If don't know please specify it)*

4) Do you remember if during the “motion event” that triggered MdDS, you were under medications or where you having your menstrual cycle?

5) Dates of motion event and the date of the first appearance of the symptoms:

6) What were your initial symptoms? *(eg., rocking, swaying, bobbing, walking like if you were on a trampoline, head pressure, brain fog, disorientation, visual disturbance, light sensitivity etc)*

7) Do you still have the same symptoms/disabilities nowadays? *(Specify if they are worst or better and if you remember when they changed)*

8) Are your symptoms persistent or do you have changes according to different days? *(Describe the fluctuations and if the changes are related to particular events: stress, menstrual cycle)*

9) How do you rate your current severity of MdDS on a scale of 10 (0- symptoms free, 5- moderate, 10- most severe)?

10) How much does MdDS impair your lifestyle? *(Mention something you were able to do and now you have stopped or have difficulties)*

11) When you are standing, do you have a **constant** sense of rocking? (*If yes please specify in which direction – back to front, side to side or up to down (bobbing), and which one prevails.)*

12) Are you feeling better or normal when you are riding in a car or being re-exposed to passive motion (for example: boat or train)? *(If aware of any other factor that can make you feel better, please specify it)*

13) Have you noticed any trigger factor that makes your symptoms worst? *(For example: car ride, coffee or alcohol/ particular drinks, working on a computer, store lines in big shops, watching movies, weather changes, stress etc)*

14) Have you ever had motion sickness before the MdDS?If yes when? *(eg: Nausea, sweating, headache)*

15) Do you have migraine? Or have you ever suffered from migraine?

16) Do you suffer from other balance or hearing symptoms (Meniere's Syndrome, Vertigo or Dizziness, Otosclerosis, Hearing loss, Balance Problems)?

17) Have you had Lyme disease? *(If yes, test done date: ……..)*

18) Have you ever suffered from Sleep Disorders? (Please mention if you have ever been diagnosed with Obstructive – Central Sleep Apnea)

19) Do you feel ease while asleep?

20) Do you fall asleep easily?

21) How many hours do you sleep per night?

22) Do you feel anxious since MdDS appeared? *(Describe your mood and feelings in few words)*

23) Do you feel worst when eating products containing Glutamate?

24) Have you undergone physical therapy for your condition?

25) Would you like to complete a Diary for studying hormonal imbalance and potential MdDS symptoms aggravations?

Additional comments from the patients:

If willing to complete the diary follow the instructions below:

- ✓ Complete the attached diary everyday for two months before returning it us.
- ✓ Complete the diary every day at the same time (if possible) preferably at the end of the day, so you can describe how you felt during the day.
- ✓ Please pay particular care in mentioning the starting day of your menstrual cycle.
- ✓ If aware of your ovulating period, please do not hesitate to mention it in the diary.
- ✓ Roughly around 2months after your first note on the diary return the form to us via email.

Do not hesitate to contact us for any enquires

Contacts:

Drs.Viviana Mucci
Ph.D. Student Antwerpen University Hospital

Phone: +3238213307

E-mail: (PLEASE SEND IT TO BOTH EMAIL ADDRESSES – specifying MdDS in the email title)
morien.pauwels@ugent.be
viviana.mucci@uantwerpen.be

Office: Antwerp University Hospital (UZA)
Wilrijkstraat 10 (route 71, B904)
2650 Edegem (Antwerp)
Belgium

7.4 Extra questionnaire (treatment)

MOTION SICKNESS SUSCEPTIBILITY (Golding, 2006)

Please complete the following table by crossing the right box:

1. **As a child (before age 12),** how often you **felt sick or nauseated** (tick boxes)

	Not Applicable - Never Traveled	Never Felt Sick	Rarely Felt Sick	Sometimes Felt Sick	Frequently Felt Sick
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big Dippers, Funfair Rides					
	t	0	1	2	3

Your experience over the last 10 years (approximately), for each of the following types of transport or entertainment please indicate

2. **Over the last 10 years,** how often you **felt sick or nauseated** (tick boxes)

	Not Applicable - Never Traveled	Never Felt Sick	Rarely Felt Sick	Sometimes Felt Sick	Frequently Felt Sick
Cars					
Buses or Coaches					
Trains					
Aircraft					
Small Boats					
Ships, e.g. Channel Ferries					
Swings in playgrounds					
Roundabouts in playgrounds					
Big Dippers, Funfair Rides					
	t	0	1	2	3

Past Medical History:

Please list any surgeries, injuries, or broken bones with the dates:

Have you ever been exposed to any toxic substances (please list with dates)?

Have you ever taking any medications for nerves, depression, sleep, or nausea (please list with dates)?

Family History

Mother's history:	Father's history:
Current Age (if alive):	Current Age (if alive):
If dead, age of death:	If dead, age of death:
Cause of death:	Cause of death:
Any other medical issues?	Any other medical issues?

Siblings? List first names, ages, and health and eventual death status.

Any other diseases that run in the family (i.e. diabetes, high blood pressure, mental disease, writer's cramp, vertigo, tremors, Parkinson's disease, or something like your present condition)?

Social History/Occupational Risks

Are you presently employed?

If not: what was your previous occupation?

Do you have a relationship?

Do you have children? *(if yes list name, age, gender)*

Who lives with you at home?

Smoking history: *(if stopped mention when, and if smoking or smoked mention quantities)*

Drinking history *(if never = mark as 0; other specify quantities per week):*

Have you ever used drugs? *(state type and if still consuming)*

Gynecological history:

First day of the last menstrual period (best estimate):

State name of contraceptive if used:

Is your period regular?

Do you notice any big changes before your period?

Please circle the following symptoms if occurring:

- *Hunger for carbs,*
- *Skin disorders,*
- *Bloated,*
- *Increase in water retention,*
- *Pain in the lower abdominal area,*
- *Migraine (state when, before or during your menstrual cycle)*
- *Do you ovulate normally?*

Have you ever had a miscarriage, abortion, or complicated pregnancy?

Medications

List your current medications, why you take them, date you started them, response, and side effects if any:

List past medications, why you took them, date you started and stopped them, response, and side effects if any:

List any allergies to medications and your reaction to the medication:

7.5 VAS

Visueel Analoge Schaal-score

Hoe zou u uw Mal de Debarquement klachten scoren?

Geen klachten Ergste klachten voor te stellen