Compensatory strategies after an acute unilateral vestibulopathy : a prospective observational study

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Abstract

Purpose: In case of an acute unilateral vestibulopathy (UVP), compensatory strategies such as restoration and adaptation will lead to a decrease in intensity of the symptoms. Although measurements of compensatory strategies are available, currently an overview taking the different strategies into account, is lacking. The objectives of this study are to explore compensatory strategies and to investigate the association between compensation strategies and patient characteristics.

Methods: Restoration was objectified by the vestibulo-ocular reflex (VOR) gain on the video head impulse test and adaptation - consisting of visual, multisensory and behavioral substitution – was objectified by the Visual Vertigo Analog Scale (VVAS), Antwerp Vestibular Compensation Index (AVeCI) and Perez and Rey score (PR-score) respectively. Adequate restoration and adaptation levels were interpreted as follows: VOR gain > 0.80, VVAS ≤ 40%, AVeCI > 0 and PR-score ≤ 55.

Results: Sixty-two UVP-patients, 34 men and 28 women, were included with an average age of 52.1 ±17.3 years. At 10.5 ±1.4 weeks after onset , 41.9% of the UVP-patients reached adequate restoration levels and 58.1-86.9% reached adequate adaptation levels. Furthermore, significant associations were found between (1) restoration status and UVP-etiology (Odds Ratio (OR) with 95% CI: 4.167 {1.353;12.828}) and balance performance (OR: 4.400 {1.258;15.386}), (2) visual sensory substitution status and perceived handicap (OR: 8.144 {1.644;40.395}), anxiety (OR: 10.000 {1.579;63.316}) and depression (OR: 16.667 {2.726;101.896}) and (3) behavioral substitution status and balance performance (OR: 4.143 {1.341;12.798}).

Conclusion: UVP-patients with adequate compensatory strategies presented with better balance performance, lower perceived handicap and lower anxiety and depression scores.

Keywords

Acute Unilateral Vestibulopathy, Vestibular Compensation, Restoration, Adaptation.

1. Introduction

Optimal balance performance during daily life requires an adequate interaction between the afferent signals of the vestibular, visual and somatosensory systems [1]. A sudden partial or complete loss of vestibular function, for example after a unilateral vestibulopathy (UVP) [2], causes a visuo-proprio-vestibular mismatch of the afferent signals leading to symptoms such as vertigo or nausea. Additionally, impaired vestibular reflexes, such as the vestibulo-ocular and vestibulo-spinal reflexes (VOR, VSR), lead to spontaneous or movement induced gaze instability and unsteadiness. Central vestibular compensation refers to the mechanisms (processes) that can lead to a reduction of these static and dynamic signs and symptoms. The static signs such as spontaneous nystagmus or a postural ipsilesional tilt resolve once a new balance is found between the activity of both vestibular nuclei, whereas the recovery of dynamic symptoms requires complex compensatory strategies that involve different brain regions [3]. These compensatory strategies encompass *restoration*, *adaptation*, and *habituation*[3]. *Restoration* is defined as the return to a normalized VOR gain which can be measured by the video head impulse test (vHIT) [4]. The normalization of the VOR gain can be attributed to the repair of the vestibular sensory synapses [3,5]. Note that in literature the return to a normalized VOR gain or normalized vestibular function is sometimes referred to as adaptation [6]. However, since linguistically the word adaptation seems more fitting for processes linked to substitution, in this study the return to initial vestibular function is referred to as restoration. *Adaptation* is defined as various forms of substitution where the altered vestibular input is partially replaced by a renewed and balanced use of visual and/or proprioceptive input [3,7,8]. An example of an adaptation process was seen after unilateral labyrinthectomy in Guinea pigs where an increased spinal input was found on the lesional side [7]. If the substitution led to a rebalanced use of visual and proprioceptive input, UVP-patients should be able to cope with challenging visual and proprioceptive tasks. Hence, measuring how UVP-patients perform on such tasks, provides valuable information on adaptation. Adaptation relies on the concepts of brain plasticity and sensory reweighting [8]. In case of UVP the brain reweighs the input of the vestibular, proprioceptive and visual sources. When successful, a new balanced sensory input is perceived, free from visuo-proprio-vestibular mismatch. However, in case of an inadequate sensory reweighting, the visual input might be overweighted leading to visual dependence [9,10]. If so, patients tend to be more dependent on their vision and when in presence of a busy or conflicting visual environment, for example standing alongside a waterfront, symptoms such as dizziness are triggered. This phenomenon is referred to as visually induced dizziness or visual vertigo and can be assessed by the Visual Vertigo Analog Scale (VVAS) [11]. In case high levels of visually induced dizziness are present in UVP-patients, the

adaptation process failed. Sensory substitution can also be estimated by measuring multisensory processing during balance tasks where an increased and balanced use of proprioceptive input is expected to substitute the altered vestibular input, for example standing on a foam cushion with eyes closed. If patients experience difficulties with such tasks, inadequate adaptation was reached. Adaptation not only consists of sensory substitution but behavioral substitution as well [3]. Behavioral substitution also relies on brain plasticity and leads to behavioral adaptations to compensate for the deficient VOR function. For example, to avoid experiencing oscillopsia, changes in oculomotor behavior such as corrective saccades will occur, a blink reflex might develop or patients might avoid head movements [3,12,13]. Therefore, objectifying the pattern of the corrective saccades - with for example the Perez and Rey score (PR score) which is an outcome measure of the vHIT [14,15] - unravels information regarding behavioral substitution strategies. The faster and more organized the corrective saccades occur, the better the deficient VOR gain is compensated for. In summary, adaptation can be categorized by visual sensory substitution (e.g. VVAS), multisensory substitution (e.g. static balance tasks) and behavioral substitution (e.g. PR score). *Habituation,* the third compensatory strategy, was defined as the phenomenon of lowering the response to provoking movements due to repeated exposure. This process can be explained by a loss of post-synaptic amplitude of the neurons due to the repetition [13]. Habituation can be assessed by quantifying the response to triggers that elicit the symptoms such as head rotation, e.g. using the Motion Sensitivity Quotient (MSQ) [16]. In this questionnaire, the patient is asked to rate the intensity and duration of symptoms after performing a provoking movement. Hence, the response to these challenging movements can be objectified by the MSQ. However, habituation has been suggested to play a less significant role in the healing process compared to restoration and adaptation [3,17]. Furthermore, the compensatory strategies seem most efficient during the first weeks post onset. Nevertheless the strategies are not completed overnight. Based on animal and brain imaging studies, the compensatory strategies seem active during several months after a UVP [3]. Therefore, when assessing the compensation status, a time period of at least one to three months should be considered. Also, the investigation of levels of restoration and adaptation are especially important. The aforementioned compensatory strategies can be stimulated by vestibular rehabilitation [18-20]. Despite vestibular rehabilitation, both the duration and level of recovery vary amongst patients [3] with the possible presence of persisting symptoms. A recent review revealed chronic dizziness and imbalance in UVP patients in respectively 98 and 81% [21]. However, this variation in degree of compensation remains poorly understood. Assessing the occurrence of restoration, adaptation and habituation after an acute UVP might lead to more insights.

As currently there is no comprehensive overview of how UVP patients perform on the different compensatory strategies, it is unknown whether an association exists between compensatory strategies and symptoms such as dizziness or imbalance. Investigating the association between both might lead to a better comprehension of the development of chronic symptoms after a UVP. Furthermore, it is unclear whether the compensation status on one or more of the strategies influences chronic symptoms and functional outcome in UVP patients. Valuable insights into clinical decision-making can be obtained by investigating whether focusing on only on or two compensatory strategies leads to similar results as stimulating vestibular compensation as a whole. Therefore, we aim at gaining more insights in the healing process in case of a UVP, by formulating the present research questions as follows: (1) How many patients show adequate restoration and adaptation levels 10 weeks after onset of the UVP? (2) Can one identify differences of patient characteristics and functional outcome measures between adequately and inadequately compensated patients? Is there any difference in patient characteristics or functional outcome between patients showing more than two adequately compensated strategies versus those patients with two or less adequately compensated strategies?

2. Methods

2.1 Study Design and Participants

This prospective observational study was registered at clinicaltrials.gov (ID: NCT04979598) and approved by the ethical committee of the Antwerp University Hospital, University of Antwerp and Jessa Hospital (21/12/181). Acute UVP-patients were included if the diagnostic criteria of the Barany society were met (Table S1) [2] and after giving their written informed consent. Unambiguous evidence of reduced VOR function was determined by the vHIT (ICS-Impulse vHIT, Otometrics/Natus, Denmark) with following cut-off values: an ipsilesional VOR gain below 0.70 or a side difference in VOR gain of at least 0.30 [2]. In case the vHIT did not confirm the reduced VOR function, caloric irrigation was performed (Kaloristar, Biomed, Germany at the Antwerp University Hospital and Aquastar, Difra, Germany at Jessa Hospital). Bilateral bithermal caloric irrigation (with air or water) was performed with the patient in supine position and a head inclination of 30°. Cold and warm irrigation was offered at respectively 25°(air)/30°(water) and 44°C (for both air and water irrigation). Patients with a caloric side difference of 25% or more were included [2]. In case of a complete unilateral vestibular deafferentation, for example after a gentamycin injection or a vestibular neurectomy, patients were deemed eligible as well. Between May 2021 and December 2022, otolaryngologists from the Antwerp University Hospital (Edegem, Belgium), Jessa Hospital (Hasselt,

Belgium) and Rehabilitation Center Sint-Lievenspoort (Ghent, Belgium) referred patients up to 4 weeks after onset of the acute UVP (≤ 4 weeks). After giving their written informed consent, patients were included if the eligibility criteria were met (Table S1). At the moment of inclusion, patients received general instructions to be physically as active as possible and a customized vestibular rehabilitation home exercise program [22]. Based on the individual complaints of the patient, e.g. gaze instability, motion sensitivity or balance problems, the exercise program consisted of five to seven exercises on gaze stability, habituation or balance [23]. The patients were asked to perform the exercises twice a day for at least ten minutes per session. In each exercise, increasing difficulty levels were provided so that progression could be made. Supervision by a physical therapist was provided in case the patient was not able to perform the home exercises in a safe way or if prescribed so by the referring physician. Data on compensatory strategies were measured and processed at ten weeks after onset of the acute UVP. This minimum time period of ten weeks was considered necessary to measure compensation status as this complex process requires time [3]. An overview of the study protocol with all tests and questionnaires can be found in Table 1.

** INSERT TABLE 1 ABOUT HERE **

2.2 Outcome measures at ten weeks after onset of the acute UVP

2.2.1 Restoration

Restoration was defined as the return to a normalized VOR gain, measured by the VOR gain on the vHIT (ICS-Impulse vHIT; Otometrics/Natus, Denmark). During the vHIT, rapid and unexpected passive head movements (angular velocity above 150°/s) are executed while asking the patient to fixate their eyes on a stationary target. An adequate VOR enables a healthy subject to focus their eyes on the target during rapid head movements. This mechanism can be quantified by the VOR gain which is the ratio of the speed of the corrective eye movement to the speed of the head. In healthy subjects, the VOR gain is approximately 1. However, in case of an acute UVP, when a head impulse is given towards the affected side, the deficient VOR results in the eyes not maintaining their focus on the target but rather following the head movement. By consequence the VOR gain value decreases. Although a cut-off of 0.70 was applied in the diagnostic criteria of a UVP [2], based on normative data on the horizontal canal VOR gain [24,25], an adequate restoration was defined as an ipsilesional horizontal canal VOR gain > 0.80 (Table 2).

2.2.2 Adaptation: Sensory and behavioral substitution

2.2.2.1 Sensory substitution

Sensory substitution was defined as substitution of the altered vestibular input by a renewed and balanced use of visual or proprioceptive input, meaning that UVP-patients with an adequate sensory substitution were able to bear or cope with exposure to challenging visual and proprioceptive tasks. Adequate visual sensory substitution was assessed using the VVAS questionnaire [11]. The VVAS contains nine visual vertigo items, for example "Watching a Movie at the Movie Theatre", where the patient has to indicate on a scale from 0 to 100 millimeters whether or not and how intense this item provokes dizziness. Zero equals no dizziness complaints and 100 equals extreme dizziness complaints. A score, expressed in percentage (%), was attributed for each item according to the distance of the patients' indication from 0 towards 100 mm, 0 % corresponding to 0 mm and 100% to 100 mm. By processing as such, an average was calculated from all items to obtain a final VVAS score, which can be interpreted as follows: 0% = no visually induced dizziness, 0.1-40% = mild visually induced dizziness, 40.01-70% = moderate visually induced dizziness and scores >70% = severe visually induced dizziness [26]. VVAS-scores of 40% or below were considered as adequate visual sensory substitution, whereas VVAS-scores above 40% were considered as inadequate visual sensory substitution (Table 2).

Multisensory substitution was objectified using the AVeCI-index [27]. The index is based on age referenced standing balance performance in different conditions in which both visual and proprioceptive cues are gradually limited. Balance was tested in 4 different standing positions while keeping the eyes closed for a maximum of 30 seconds: (1) Romberg position while performing a Jendrassik maneuver (clasping hands while producing tension), (2) stance on a 12 cm thick, medium density foam cushion ((60 kg/cm3) measuring 45 × 45 cm (NeuroCom International Inc. Clackamas)) while performing Jendrassik maneuver, (3) tandem stance and (4) unipodal stance [28].
For each position three attempts were possible but when the maximal score of 30s was achieved during the first or second attempt, the test was ended. The best performance in each position was withheld and the sum of all these best scores was referred to as the Standing Balance Sum – Eyes Closed (SBS-EC) with a maximum value of 120 seconds. The AVeCI-index was calculated using the following formula: $AVeCI = -50 + 0.486 \times age + 0.421 \times SBS\text{-}EC$. For each patient the AVECI-index was interpreted as adequate ($AVeCI > 0$) or inadequate multisensory substitution ($AVeCI \leq 0$) [27] (Table 2).

2.2.2.2 Behavioral substitution

Behavioral substitution was defined as changes in oculomotor behavior – namely the occurrence of corrective saccades and how they are organized - to compensate for the deficient VOR function. Behavioral substitution was assessed by the PR score [14,15], which is one of the outcome measures of the ICS-Impulse vHIT (Otometrics/Natus, Denmark) [5]. The PR-score is calculated based on the temporal organization of the corrective saccades. Shortly after the UVP, it is likely that the presentation of the corrective saccades will be more scattered as the central vestibular system is not trained yet in correcting for the deficient VOR. The better and more consistent the correction occurs, the more concentrated within the same time period after head movement the saccades will be presented instead of being scattered all over. The PR-score has a minimum and maximum score of respectively 0 and 100. Per saccade group, the coefficient of variation (CV) of the timing of appearance of the saccades was calculated. Afterwards a global PR-score was calculated using following formula: 2.5*(0.8*CV1 + 0.2*CV2) with 1 and 2 representing the first and second group of saccades (both covert and overt saccades). The lower the PR-score, the more concentrated the saccades are presented (more compensated) and the higher the PR-score, the more scattered the saccades are presented (less compensated). In case no saccades are present, the PR-score cannot be calculated and is equal to zero. More details on the calculation of the PR-score are described elsewhere [14]. Previous research revealed a cut-off score of 55 with scores equal to or below 55 indicating a compensated patient and scores above 55 indicating an uncompensated patient [15]. For each of the included patients, the PR-score of the affected horizontal semicircular canal was used in the analysis as research revealed a more reliable vHIT outcome in the horizontal canals compared to the vertical canals [29,30]. Therefore, an ipsilesional horizontal PR score ≤ 55 was interpreted as adequate behavioral substitution (Table 2).

** INSERT TABLE 2 ABOUT HERE**

2.2.3 Number of adequately compensated strategies

Based on the aforementioned compensatory strategies, a total of four different strategies were listed per patient: restoration, visual sensory substitution, multisensory substitution and behavioral substitution. The patients were divided into two groups: patients that showed adequate compensation on ≤ 2 or those presenting with ≥ 3 adequately compensated strategies.

2.3 Functional outcome measures

2.3.1 Dynamic balance performance

Dynamic balance performance was assessed following an earlier prescribed protocol [28] consisting of a Tandem Gait and Timed Up and Go (TUG) test. During Tandem Gait, the patients were asked to walk heel to toe on a line. The patient was given three attempts to reach the maximum score of 20 steps. The Tandem Gait was interpreted as successful in case the maximum number of 20 steps was reached. During the TUG, the patient started from a sitting position. After an oral start command by the investigator, the patient was asked to stand up, walk three meters, turn 180°, walk back towards the chair and return to sitting position. The patient was instructed to perform the TUG as fast as possible but safely. The TUG was performed three times as well, of which the fastest time to perform the TUG was withheld in the analysis. The TUG was interpreted in relation to age: < 6, < 7 and < 8 seconds were seen as age appropriate for patients < 40 years, 40-60 years and > 60 years respectively [28].

2.3.2 Perceived Handicap due to dizziness

The Dizziness Handicap Inventory (DHI) was used to estimate the patients' perceived handicap due to dizziness [31,32]. The DHI consists of 25 questions, e.g. "Does walking down a sidewalk increase your problem?", that can be answered with no (0 points), sometimes (2 points) or yes (4 points) leading to a maximum score of 100. The higher the score, the higher the perceived handicap is present with following categories: 0-30 representing a mild handicap, 31-60 a moderate handicap and 61-100 a severe handicap due to dizziness [33]. In this study, scores were divided into two groups: no or mild handicap (DHI ≤ 30) or a moderate to severe handicap (DHI > 30).

2.3.3 Fear avoidance beliefs, anxiety and depression

Psychological factors were assessed using two questionnaires: the Vestibular Activities Avoidance Instrument (VAAI) [34,35] and the Hospital Anxiety and Depression Scale (HADS) [36]. The VAAI consists of nine items evaluating the presence of fear avoidance beliefs: e.g. "I can't do all the things normal people do because of my dizziness". Each item is rated ranging from strongly disagree (= 0) to strongly agree (= 6) leading to a maximum score of 54. The higher the score, the higher the chance of presence of fear avoidance beliefs. The HADS consists of 14 items evaluating both anxiety (7 items) and depression (7 items). Each item is rated ranging from 0-3 leading to an anxiety and depression subscore of maximum 21 points. The anxiety and depression subscores are interpreted as follows: 0-7: no anxiety or depression disorder; 8-10: possible anxiety or depression disorder; 11-21: probable anxiety or depression disorder. For each psychological factor, a cut-off value was used to categorize the patients in two groups: 18/54 on the VAAI (fear avoidance beliefs) [34], 8/21 on the subscale

anxiety and depression of the HADS (anxiety and depression) [36]. Scores above or equal to the cut-off values were interpreted as presence of fear avoidance beliefs (VAAI) or a possible to probable anxiety or depression disorder (HADS).

2.4 Statistical Analysis

Depending on the nature of the data, clinical characteristics of the patients were described using either frequencies or means and standard deviations. Descriptive statistics were performed on the different compensatory strategies as well: restoration (VOR gain), sensory substitution (VVAS and AVeCI) and behavioral substitution (PR-score). Furthermore, patients were divided in an adequately or inadequately compensated group for each compensatory strategy: compensated (VOR gain category > 0.80 [24,25], VVAS ≤ 40% [26], AVeCI > 0 [27] or PR-score ≤ 55 [15]) or uncompensated (VOR gain ≤ 0.80 [24,25], VVAS > 40% [26], AVeCI ≤ 0 [27] or PR-score > 55 [15]) group. Patient characteristics (age, sex and cause of the UVP) and functional outcome measures (dynamic balance performance (tandem gait, TUG), perceived handicap due to dizziness (DHI), fear avoidance beliefs (VAAI), anxiety and depression (HADS)) were categorized and compared between the compensated and uncompensated patients using a Chi-square tests or a Fisher's Exact test. The latter was used in case one of the cells in the contingency table reported a number below 5 [37]. Results on the Chi-square and Fisher's Exact tests were reported as the Odd Ratio (OR) with accompanying 95% Confidence Intervals (CI) and considered significant if the confidence intervals did not contain 1 in combination with a *p*-value < 0.05. The same variables were compared between patients that adequately compensated on ≤ 2 or ≥ 3 compensatory strategies using Chi-square tests or a Fisher's Exact test. All statistical analyses were performed using IBM Statistics SPSS 27 for Windows.

3. Results

3.1 Participants

Sixty-two UVP-patients, 34 men and 28 women, were included in this study with an average age of 52.1 years (± 23.6). The vestibulopathies had an inflammatory etiology in 36 cases (e.g. vestibular neuritis or labyrinthitis) as opposed to an iatrogenic or traumatic etiology in 26 other cases. Iatrogenic etiologies were those in which the acute vestibulopathy occurred due to surgical procedure, e.g. a vestibular neurectomy during resection of a vestibular schwannoma. More details on the etiologies can be found in Table 3. In 32 of the 62 patients, the affected side was the right side. At the moment of inclusion, range of one to four weeks after onset of the UVP, the ipsilesional VOR gain was 0.59 (± 0.24) with an average VOR gain side difference of 0.37 (± 0.22). In case patients did not meet the criteria of the Barany society based on the VOR gain, results on caloric testing were

extracted from the patients file. In 22 patients, the caloric side difference resulted in an average caloric asymmetry of 66.7% (± 32.2). At ten weeks, patients reported an average daily practice time of 15.8 (± 19.4) minutes. Twenty-four patients followed supervised physiotherapy sessions besides performing the daily home exercises.

** INSERT TABLE 3 ABOUT HERE**

3.2 Overview of the compensatory strategies at 10 weeks after onset of the UVP

At 10.5 (±1.4) weeks after onset of the UVP, 41.9% of the patients (n= 26) had a VOR gain value above 0.80 indicating that these patients reached sufficient restoration levels (Figure 1). The remaining patients showed a VOR gain of 0.80 or lower (58.1%, n=36). As for sensory substitution, the VVAS-scores of 61 patients (missing VVAS-score in one patient) revealed that 86.9% (n= 53) of the patients presented with adequate visual sensory substitution levels. Based on the AVeCI-index, 74.2% of the patients (n= 46) showed adequate multisensory substitution levels. Moreover, PR-scores of 55 or below were obtained in 36 patients, indicating that 58.1% of the patients achieved adequate behavioral substitution levels. In summary, the results indicate that 58.1– 86.9% of the patients had attained adequate adaptation levels after a period of 10 weeks (Figure 1).

** INSERT FIGURE 1 ABOUT HERE**

3.3 Comparing characteristics and functional outcome measures based on compensatory strategy levels

3.3.1 Compensatory strategy levels

Restoration status was significantly associated with the cause of the UVP and tandem gait scores. Among patients who achieved a sufficient restoration level (VOR gain > 0.80), there was a higher-than-expected prevalence of inflammatory causes and maximal tandem gait scores (OR: 4.167, 95% CI 1.353-12.828, p: 0.011 ; OR: 4.400, 95% CI 1.258-15.386, p: 0.016). Regarding visual sensory substitution, significant associations were found with perceived handicap and anxiety and depression scores. In the group of patients who exhibited inadequate visual sensory substitution levels (VVAS > 40%), there was a higher-than-expected prevalence of moderate to severe perceived handicap and possible to probable anxiety and depression disorder (OR: 8.144, 95% CI 1.644-40.395, p: 0.012 ; OR: 10.000, 95% CI 1.579-63.316, p: 0.025 ; OR: 16.667, 95% CI 2.726-101.896, p: 0.004). Based on multisensory substitution, no significant associations with patient characteristics or functional outcome measures were found. Finally, patients with a PR score below 55 – indicating an adequate

behavioral substitution - showed a significantly higher-than-expected percentage of maximal tandem gait scores (OR: 4.143, 95% CI 1.341-12.798, *p*: 0.011) (Table 4, Figure 2).

INSERT TABLE 4 ABOUT HERE

3.3.2 Number of adequately compensated strategies

In regard to the number of adequately compensated strategies, significant associations were found with cause of the UVP and tandem gait scores (Table 5, Figure 2). A significantly higher-than-expected prevalence of inflammatory etiologies was found in the group that adequately compensated on at least three different strategies (OR: 4.160, 95% CI 1.419-12.192 *p*: 0.010), likewise for maximal tandem gait scores (OR: 3.000, 95% CI 0.998-9.020, *p*: 0.047).

INSERT TABLE 5 AND FIGURE 2 ABOUT HERE

4. Discussion

Summary and discussion of the findings

After an acute UVP, it is expected that compensatory strategies take place leading to a gradual decrease of symptom intensity. Restoration, adaptation and habituation have been identified as compensatory strategies. In this study, adequate restoration levels were obtained in less than half of the patients. The majority of the adequately restored patients (76.9%) had an inflammatory cause of the UVP. Besides inflammatory causes, iatrogenic and traumatic causes of a UVP were included as well. In 18 of the iatrogenic cases, a vestibular neurectomy was performed which resulted in a complete and irreversible loss of vestibular function. Although specific gaze stability exercises enhance dynamic visual acuity in these patients, previous research revealed that after a vestibular neurectomy, a restoration of VOR gain seems unattainable [38]. In addition, VOR gain as an evaluation of restoration status might be a less conclusive outcome measure after a complete and irreversible loss of vestibular function such as after a vestibular neurectomy [17]. In summary, the inclusion of both inflammatory and iatrogenic causes of a UVP might explain the rather low number of adequately restored patients in this study. Besides more inflammatory causes, the group of adequately restored patients, showed significantly more maximal tandem gait scores, suggesting that an adequate VOR gain leads to an improved dynamic balance performance. However, this was the case for only one of both dynamic balance tests (Tandem Gait and not the TUG) suggesting that the Tandem Gait is more sensitive compared to the TUG. However, previous research revealed similar receiver operating characteristic (ROC) values to screen for vestibular impairments for both Tandem

Gait and TUG with respectively 0.75 [39] and 0.70-0.90 for the TUG depending on the age group [28]. Furthermore, in literature, conflicting evidence is present regarding the relation between balance performance and VOR function [40,41], indicating that more research is needed to further elaborate on the association between both. Maximal tandem gait scores were also significantly associated with adequate behavioral substitution levels, based on the PR-scores. These results suggest that not only VOR gain but also the temporal organization of the corrective saccades help to perform dynamic balance tasks. Again, this was only the case for Tandem Gait and not for TUG scores. Literature confirms that the organization of the saccades is important regarding visual acuity, its effect however on balance has not been studied up to our knowledge [42,43].

Adequate adaptation levels were reached in the majority of the patients after a period of 10 weeks (58.1-86.9%). Moreover, the significant associations found between adaptation levels and balance performance, perceived handicap and anxiety and depressions scores emphasize the importance of assessing adaptation levels and taking the results into account in clinical decision making. The relation between visual sensory substitution and perceived handicap has been identified before [44] which seems plausible as an inadequate visual sensory substitution will lead to more impairments in daily life. Furthermore, in case of UVP, the sustained visuo-proprio-vestibular mismatch might lead to higher levels of anxiety and on the long-term depression as was explained by an internal-fake-news-model [45]. Therefore, in case VVAS scores reveal an inadequate visual sensory substitution, visual desensitization exercises seem relevant to offer so that long term distress due to repeated disturbed multisensory integration can be avoided. If visual desensitization exercises such as optokinetic training are applied, literature suggests that (1) optokinetic training is better compared to no intervention, (2) in combination with vestibular rehabilitation it leads to additional benefits and (3) when offered supervised, optokinetic training is superior to unsupervised optokinetic training [46-49].

Finally, it seems important not to focus on the assessment and treatment of only one type of compensatory strategy. Our results confirm that patients that reached adequate compensation levels on at least three different strategies had a higher-than-expected-prevalence of maximal tandem gait scores. In addition, a (not significantly) higher prevalence of favorable dizziness scores was found in these patients as well. Based on the assessment of the different strategies, targeted exercises can be integrated into a vestibular rehabilitation program to facilitate all possible compensation strategies. For example, exercises on balance and visual desensitization influence the processing of proprioceptive and visual input and therefore lead to improvements in visual and multisensory

substitution whereas exercises on gaze stability will rather result in improved behavioral substitution and restoration [18,19,50]. In addition, a higher-than-expected number of inflammatory causes was found in the patients with at least three adequately compensated strategies. These results indicate that having an inflammatory cause of the UVP results in a higher chance of achieving at least three adequately compensated strategies within a period of 10 weeks. Further research with a longer follow up period is recommended to investigate whether this larger improvement in inflammatory UVP-patients is temporary or not. Longer follow up might unveil that after a period, both groups compensate equally regardless of the cause of the UVP.

Limitations

In this study an attempt was made to cover different levels of compensation based on the vestibular compensation model of Lacour et al. 2016 [3]. However, we are aware that other approaches and assessments of vestibular compensation can be considered as well. An overview of different measures of central vestibular compensation recently came available suggesting other assessments and outcome measures such as the VOR asymmetry index (restoration), posturography (multisensory substitution) or saccade frequency (behavioral substitution) [17]. Future research in which different outcome measures for the compensatory strategies are compared, might lead to more consensus on the assessment of vestibular compensation. For example, the PR score - which was used to objectify behavioral substitution - is calculated based on the temporal organization of the corrective saccades not taking the number or amplitude of the saccades into account. Consequently, a high PR score (worse compensation) can occur when only a few, rather small saccades are present in a scattered way. Furthermore, as the PR score is a fairly new outcome measure, more research is necessary to support the proposed cut-off value of 55 [15]. Similarly, although the AVeCI-index was developed based on its relation with caloric and rotatory chair testing, it was only recently developed and should be further implemented in vestibular research to explore its ability to objectify multisensory substitution [27]. Regarding visual sensory substitution, the VVAS-questionnaire was used which is a subjective measurement. Although objective measurements are preferred over subjective questionnaires, the VVAS appeared to have the highest predictive value for identifying persistent postural-perceptual dizziness (PPPD) when being compared to more objective measurements such as the Rod & Disc test or postural sway measurements in visually destabilizing conditions [51]. Besides that, the VVAS is a user-friendly questionnaire, making it easily applicable in daily clinical practice. Another limitation is that the association found between the VVAS and DHI should be interpreted with caution as these questionnaires share an item (“Walking down the aisle of the supermarket”).

However, since the rating was different in both questionnaires (3-point scale in the DHI and a VAS-scale in the VVAS) and it concerns only one shared item, the effect is not expected to be substantial. Besides limitations in the chosen outcome measures, we acknowledge that not all aspects of compensatory strategies were covered. For example, regarding behavioral substitution, the organization of corrective saccades was measured, however the occurrence of avoidance behavior or a blink reflex to avoid symptoms was not taken into account.

Habituation as a compensatory strategy was not objectified in our study. By consequence, only two out of three compensatory strategies were covered in this study, leading to an incomplete overview of the compensatory strategies. However, as habituation was stated to be the least significant strategy [3,17], we believed it was acceptable to focus on restoration and adaptation. Moreover, in contradiction to restoration and adaptation the term habituation itself describes a reaction (habituation due to repeated exposure) rather than the underlying physiological mechanism, making it more challenging to objectively assess.

Conclusions

This study found that after 10 weeks, most participants (58.1- 86.9%) reached adequate adaptation levels, while 41.9% reached adequate restoration levels. Those with inflammatory causes of the UVP had better outcomes in terms of restoration and number of compensated strategies. Participants with adequate compensatory strategies presented with better balance performance, lower perceived handicap, and lower anxiety and depression scores. Therefore, we recommend assessing compensatory strategies to help identify patients in need for customized additional therapy such as balance or visual desensitization exercises.

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608 Figures

609 - Figure 1: Compensatory Strategy Levels after a 10 week period
610 - Figure 2: Overview Results
611 - Legend: TG= Tandem Gait, DHI= Dizziness Handicap Inventory, , TUG= Timed Up and
612 Go, HADS= Hospital Anxiety and Depression Scale. A bold black square indicates a
613 significant result on Chi-square or Fisher's Exact test.

614 Tables

615 - Table 1: Study Protocol
616 - Table 2: Compensatory strategies after acute unilateral vestibulopathy
617 - Table 3: Patient's Characteristics
618 - Table 4: Comparison of patient characteristics and functional outcome measures based
619 compensation status
620 - Table 5: Comparison of patient characteristics and functional outcome measures based on
621 number of adequately compensated strategies

622 Supplementary Information

623 - Table S1: Inclusion criteria