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Highlights

- The estimation of verticality (assessed with Subjective visual vertical (SVV)) is more variable in patients with Usher (type I and II) compared to healthy participants.
- Visual and vestibular information are essential for the visual vertical (VV) perception.
- A reweighting of sensory information from the central nervous system seems to be able to compensate for the absence of vestibular function in patients with Usher type I.

Abstract.

BACKGROUND: Verticality, or more precisely the ability to perceive spatial orientation with regard to gravity, is based on the integration of visual, vestibular and somesthetic information.

OBJECTIVE: The purpose of the present study was to compare the subjective visual vertical (SVV) in patients with Usher (type I and type II) with visual or vestibular impairment, and in healthy participants, in order to explore the importance of the visual and vestibular functions on the vertical's perception.

METHODS: We evaluated the SVV using a wall housing which projects on the opposite wall a red-light line of about 2 meters, obtained by laser cannon. The evaluation was carried out under two tilt conditions: clockwise and counter-clockwise randomly performed five times in each direction. The response to the SVV task was quantified by the mean of the absolute values of the SVV.

RESULTS: Responses to the SVV were significantly less accurate in patients with Usher with respect to healthy participants while it was similar for the two groups of patients with Usher.

CONCLUSIONS: We hypothesize that visual inputs play a very important role in the perception of verticality and that the symmetrical bilateral vestibular deficit in Usher type I does not have a strong impact in perception of verticality.

Keywords: Subjective visual vertical, Usher syndrome, visuo-vestibular inputs, somes- thesia, perception of space, verticality

1. Introduction

Usher's syndrome was first described by Von Graefe in 1858. It is characterized by a sensorineural hearing loss, a retinitis pigmentosa (RP, which is a genetic retinal degenerative disease leading to a progressive loss of the peripheral vision and ultimately

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blindness) and, in some cases, a vestibular dysfunction. Its heritability was established by Charles Usher, a British ophthalmologist [19] Nine causative genes have been identified and three clinical types are known, depending on the severity of the hearing loss. Type I is characterized by a severe congenital hearing loss with congenital vestibular dysfunction and a RP usually diagnosed the first decade; Type II combines a moderate congenital hearing loss, normal vestibular function and RP diagnosed in the second or third decade, and type III, the rarest type, is characterized by a late progressive deafness [6]. Usher syndrome is relatively rare in the population, with an incidence rate of 4 births per 100.000 [24]. These patients face a progressive multisensory disability (particularly visual) that leads to a gradual loss of control of balance and autonomy in activities of daily living.

Verticality, or more specifically the ability to perceive spatial orientation in relation to gravity, is essential to maintain the posture and to perform most of motor activities. Verticality is based on the integration of visual, vestibular and somesthetic information [12] and the influence of visual information on the perception of subjective vertical visual (SVV) has been known for many years. Witkin and Asch [28], asked healthy subjects to estimate the position of a rod within a 22° tilted frame (Rod and Frame Test) and they found that the tilted frame affected the subjects' perception of vertical. The subjects tended to perceive the rod to be tilted by a mean of 15° in the direction of the inclination of the frame but not all of them were sensitive to the inclination of the frame. The authors then suggested that subjects who make errors in estimating the verticality when visual context is tilted were dependents of visual cues or field-dependent.

Another example of the importance of visual information on the perception of verticality is the modification of the evaluation of the SVV in the presence of optokinetic stimuli (i.e. projection of a moving or rotating visual scene). Guerraz et al. [9], observed a deviation of SVV in the direction of the movement of the visual scene in the presence of optokinetic stimulation.

Somesthetic information also plays an important role in the perception of the subjective vertical. Trousselard et al. [23], showed that the suppression of somesthetic information by placing subject in an "emergency transfer vacuum mattress" increases the perception of tilted verticality when their body is tilted more than when there are not immobilized.

Vestibular inputs are also important for the SVV estimation. The vestibular system is the only specific sensory input coding for the gravitational acceleration. Stimulation or destruction of the vestibular system causes a change in the sense of verticality [2]. The vestibular system is sensitive to linear and angular accelerations of the head. It informs the central nervous system of the orientation of the head according to gravity and gives information about head movements in space (static and dynamic information) [17]. The impact of vestibular impairment on the perception of SVV has been the subject of multiple studies in unilateral vestibulodeficient patients; these studies have shown that the SVV is tilted to the side of the vestibular lesion [25, 4].

Lopez et al. [18], compared the performance of SVV under two visual conditions: static visual environment and clockwise and counter-clockwise optokinetic stimulation in three groups of adults, a group with unilateral vestibular loss, a group with bilateral vestibular loss and a control group. The authors showed that when vestibular loss was unilateral, SVV was tilted to the injured side, independently of visual conditions (static or dynamic); in case of bilateral vestibular loss the estimation of SVV was not affected in the static visual condition, but was affected in the presence of optokinetic stimulation. The authors suggested that in static visual condition patients primarily solicit visual information to compensate their loss of vestibular information allowing a correct estimation of SVV; however, in the dynamic visual condition this was not possible because the visual information was disturbed.

When vestibular afferents are lacking, the sensory system could compensate using the other sensorial inputs; note, however, that such impairment has very different consequences when it is acquired and when it is congenital; indeed frequently subjects with congenital or early vestibular dysfunction are well compensated, whereas subjects with acquired vestibular loss are poorly compensated [22]. Patients with Usher have both congenital deafness and, in some cases, a vestibular dysfunction but they also present a visual deficit that could get worse during the life leading to more complex reorganization of the neuroceptive system. An important methodological question is how to analyze the results of SVV, since in all these studies the authors calculated the mean of numerical values of SVV while more recently, Funabashi et al. [7], showed that in patients with bilateral vestibular deficiency, SVV performances are abnormal only when the absolute values of SVV was considered.

Table 1
Clinical characteristics of patients with Usher type I and type II (means ± standard errors). The vestibular status is indicated as: complete vestibular areflexia (CVA), partial vestibular deficit (PVD) and normal vestibular function (NVF). The visual field evaluation is shown as the percentage of the peripheral visual field (PVF) and central visual field (CVF) present for each patient. DHI correspond to the score at the Dizziness Handicap Inventory (0 is the best score and 100 is the worst)

	Age (year)	Vestibular screening	Peripheral visual field (% all peripheral field)	Central visual field (% of all Central Field)	DHI-score (total 100)
Usher type I	24.8 ± 2.4	75% PVD 25% CVA	24.7 ± 5.7	99.2 ± 0.8	30 ± 3.5
Usher type II	39.8 ± 2.8	100% NVF	35.4 ± 7.2	90.5 ± 4.7	8.4 ± 1.8

The aim of the present study was to evaluate the role of visual and vestibular information on the SVV perception by studying two groups of patients with Usher (type I and type II) that differs by their vestibular function, severely impaired on both sides symmetrically in Usher I and normal in Usher II, while they both have progressive visual impairment. We hypothesize that vestibular and visual loss may have different roles in estimating SVV.

2. Materials and Methods

2.1. Participants

This study was conducted in two groups of patients with Usher (genetically identified for their type). The first group was composed of 24 Usher type I patients (mean age: 24.89 ± 11.6 years) and the second of 21 Usher type II patients (mean age: 39.84 ± 13.26 years). A third group of 20 healthy control participants aged between 20 and 42 years (mean age: 26.6 ± 5.5 years) was also included in the study. Note that the Usher type I patients were younger than the Usher type II patients because the onset of visual impairment in Usher type II occurs latter than in Usher type I which delays the diagnosis.

A complete vestibular testing battery including semicircular canals and otolith systems, was done on all patients with Usher (type I and II). The canal function was evaluated for different velocities: video head impulse test (vHIT) for high velocities, bithermal caloric test for low velocities, Earth Vertical Axis Rotation test (EVAR) for middle velocities. The otolith function was assessed with cervical Vestibular-Evoked Myogenic Potential (c-VEMP). A clinical neurological examination and an audiologic evaluation were also performed [27, 14].

An exclusion criterion for Usher (type I, II) was the lack of molecular diagnosis of Usher's syndrome and monocular corrected visual acuity (tested at far distance with the Snellen chart) $\leq$0.5 LogMa.

For each participant an ophthalmologist measured the binocular visual field by using the Goldmann perimetry test. In order to quantify the degree of visual impairment binocular visual field charts divided by radial lines (separated by 15°) and concentric lines (separated by 10°) were used. We obtained 424 compartments. We counted the number of compartments, for each patient, which were surrounded by the zone of visual sensitivity (isopters) of the patient for the central and the peripheral visual fields. The results were expressed as a percentage of the entire visual binocular field. The peripheral visual field, in the chart, corresponded to the area of vision in an annulus extending from 10 to 90° radii. A radius of 10° from the center of the area of vision is equivalent to the central visual field. The percentage of the entire field corresponded to the effective visual field present for each patient. The Dizziness Handicap Inventory (DHI) questionnaire scoring from Jacobson and Newman [13] was used in order to study the impact of the vestibular deficit of the patients with Usher on daily live (see Table 1). Following Whitney et al. [26] patients with Usher were classified as mild, moderate and severe functional impairment if the score at the DHI questionnaire ranged between 0–30, 31–60, or 61–100, respectively. One Usher type I patient only had a severe functional impairment while the other Usher type I patients showed mild (13/24) or moderate (10/24) functional impairment. In contrast all Usher type II patients reported a low score at the DHI questionnaire and all of them had mild functional impairment.

All healthy participants were recruited in Robert Debré Hospital (staff members and trainees) and were exempt from motor, vestibular and visual disorders.

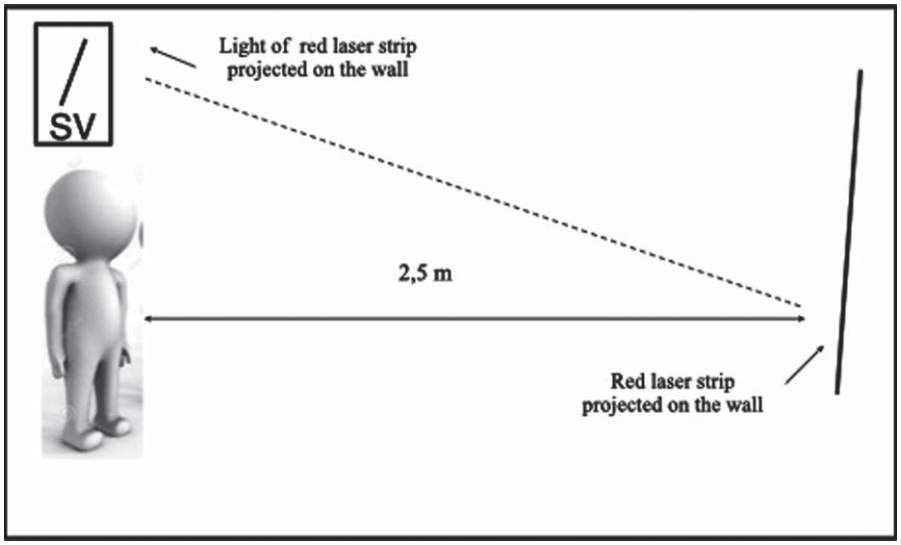

Fig. 1. Experimental set up.

Exclusion criteria were: presence of neurological disorders, visual impairment, vestibular disorder or orthopedic disorder or surgeries.

The investigation adhered to the principles of the Declaration of Helsinki and was approved by our Institutional Human Experimentation Committee (Comité de Protection des Personnes CPP, Ile de France). After the procedure had been explained, a written informed consent was obtained from the participants and their parents when the participants were under the age of 16-year-old.

2.2. Experimental procedure

In a darkened and sound-insulated room a red laser stripe of about 2 m height is projected on a white wall, at a distance of 2.50 m from the standing subject and the center of the stripe at the level of the patient's eyes (see Fig. 1). The laser strip is silently rotated via a remote control by the experimenter (the subject did not control the rotation in order to avoid haptic cues). The stripe first appears oriented vertically. Then the patient is asked to close his eyes. The experimenter (standing just behind the patient with the computer) tilts the stripe 15° clockwise or anti-clockwise in a random sequence, and then the patient is asked to open his eyes. The stripe is slowly rotated back at 2°/s, toward the vertical orientation. The participants is instructed to signal verbally or in case of profound hearing loss and sign language with a sign of his/her choice (acoustic or visible by the experimenter by means of the subdued light given by the computer) as soon as they perceived the laser line to be perfectly vertical, and this orientation was recorded. Five trials were performed in each direction for each subject [8]. Note that during the experimental procedure participants was unable to see anything in the room except the laser line on the wall.

Before the recorded trials, the SVV test was precisely explained (with a sign language translator if needed), and all participants were trained with a few trials in order to be sure that they understood the test. During the test, the participants stand on a stable platform, with their arms resting at their sides. The position of their feet is on the footprint marks on the platform, heels separated by 2 cm and feet angled of 15° symmetrically with re-spect to the sagittal axis. The participants are instructed to remain stable, avoiding any voluntary movement.

2.3. Data and statistical analyses

The SVV value indicates the angle (in degrees) between the SVV and the objective gravitational vertical. For each participants, in the two conditions (CW and CCW), we calculated the mean absolute value of the SVV and its variability with standard error and sample variance (see Table 2).

After testing the normality of data, ANOVA (Statistica software) was carried out on the absolute mean values of SVV, for clockwise direction and counter-clockwise direction, for the two groups of patients

with Usher (type I and type II) and the group of healthy participants. In case of significant effects, *Post-hoc* comparisons were made using the *post-hoc* Bonferroni test. The effect of a factor was considered significant when the *p*-value was less than 0.05. All our samples follow a normal distribution (Kolmogorov-Smirnov test; alpha > 0.05).

3. Results

Figure 2 shows the distribution of the mean absolute values of SVV and interquartile ranges for the three groups of participants. ANOVA showed significant group effect ($F(2,62) = 9.75$, $p < 0.0002$); the *post-hoc* Bonferroni test showed that the SVV value was significantly greater in Usher type I patients compared to healthy participants ($p < 0.0001$); also Usher type II patients showed significantly greater variability in SVV values than healthy participants ($p < 0.002$). Finally, there was also a small difference of SVV variability between patients with Usher type I and Usher type II and this difference did not reach statistical significance ($p > 0.2$). Similarly, we did not observe any significant difference between the two inclinations (clockwise versus counter-clockwise, $F(1,62) = 0.53$, $p = 0.4$). Furthermore the ANOVA on the variances between the trials (see Table 2) reported a significant group effect ($F(1,62) = 10.68$, $p < 0.001$) and the *post-hoc* Bonferroni test showed that the variance of the patients with Usher type I and II was significantly higher to that reported in healthy participants ($p < 0.0001$).

Finally, we failed to show any correlation between the DHI score and the SVV performance.

4. Discussion

The main results of this study were: i) The estimation of verticality (assessed with SVV) is worse in patients with Usher (type I and II) compared to healthy participants; ii). The perception of SVV is similar in Usher type I and type II, however the value of SVV is more variable in Usher type I patients than in Usher type II but this difference is not statistically significant; iii) Similar to healthy participants, the SVV estimation in patients with Usher does not depend on the presentation of the line (CW, CCW). In the following we will discuss in detail these results.

4.1. The estimation of verticality (assessed with SVV) is more variable in patients with Usher (type I and II)

The greater variability of estimation of SVV observed in patients with Usher suggests that perception of SVV is controlled by vestibular as well as visual information, in line with the study of Lopez et al. [18]. The slightly greater SVV variability observed in Usher type I compared to Usher type II (not reaching statistical significance) could suggest a small impact of the vestibular bilateral symmetrical loss on perception of SVV that could be partially compensated. However, the vestibular loss of patients with Usher type I is congenital and we suspect that their multisensory compensatory systems are fully completed (particularly because their vestibular loss is profound and stable). In contrary, the visual impairment in all Usher types is progressive due to the extension of the retinitis and consequently compensation processes have to be updated permanently and can never be completed. This will explain why Usher type I and Usher type II present the same variability of their SVV. Note however, that the variability was significantly larger in both groups of patients (Usher type I and II) with respect to control group, most likely due to a central vestibular dysfunction [5].

The increased variability of the SVV observed in patients with Usher may be associated with an underlying central disorder. Henricson et al. [10] showed lower cognitive skills of patients with Usher compare to patients with deafness and cochlear implants (tasks of phonological working memory and phonological skill).

These findings are consistent with the hypothesis of a central disorder in Usher patients that could also explain a poor vertical visual perception.

Our study is the first to study the role of a peripheral visual impairment on the SVV estimation. It is well known that the central vision is the most important input for the SVV estimation. However, peripheral vision is important during everyday life for the cognitive and memory representation of the vertical perception [1, 15]. This hypothesis is also in line with studies [16, 20], showing poor postural control when peripheral vision is defective (i.e. glaucoma). Moreover, Horiuchi et al. [11], emphasized the role of the peripheral vision on postural stability for quiet standing because moving visual surrounding (with opto-cinetique stimuli) that stimulate principally the peripheral visual field perturbed postural stability in normal subjects. Patients with Usher type I and type II

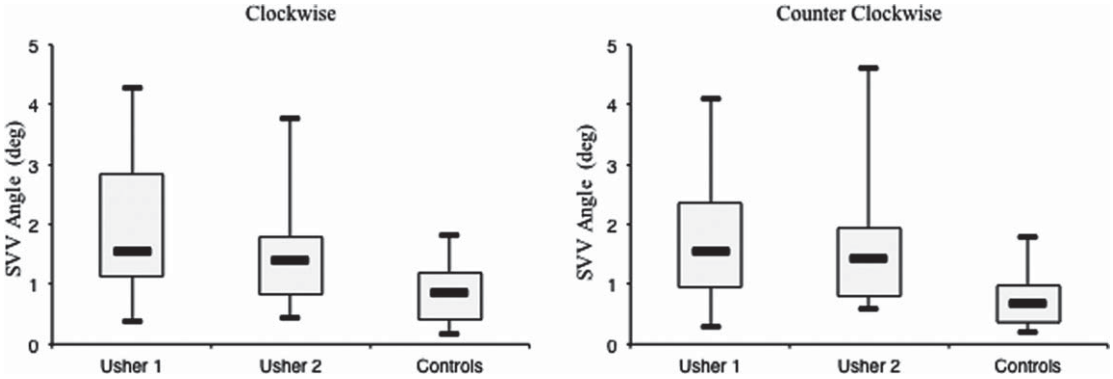

Fig. 2. Box-plot showing the distribution of the absolute values of the SVV in the two tilts conditions (clockwise and counter-clockwise) for the three groups of participants: median with the inter-quartile range of the SVV and minimal-maximal values.

Table 2
Descriptive statistical characteristics of the three groups of participants (Usher Type I, Usher Type II and controls): mean of the raw SVV values, sample variance, mean of the absolute values of the SVV and standard error for each group

	Mean SVV (raw measurements)	Sample variance	Mean SVV Absolute Values	Standard error
Usher type I	–0,69	2,12	1,64	0,53
Usher type II	–0,75	1,79	1,54	0,43
Controls	–0,13	0,65	0,82	0,25

are facing a progressive reduction of their peripheral visual field to a final tubular vision. Even though their retina lesions are not symmetrical they do not show lateralization of their SVV. Lateralization of SVV has been described in unilateral vestibular lesion [18] or in patients with central lesion [9].

No lateralization of the SVV was found in patients with Usher. We suggest that in patients with Usher type I it is due to the symmetrical vestibular loss. However, the retinal lesions were usually not symmetrical and this asymmetry was not found in the SVV results in our patients probably because of a central compensation. These results are consistent with earlier observations of Asch and Witkin [28] and [21], illustrating the importance of visual information on the perception of verticality.

4.2. *Visual vertical perception is slightly different between patients with Usher type I and type II*

The present study showed that the variability of SVV was more pronounced in patients with Usher type I that in Usher type II but without reaching statistical significance. This finding is in line with the study of Lopez et al. [18], showing that bilateral vestibular loss does not affect the SVV perception in static visual condition, but only in the presence of optokinetic stimulation emphasizing the importance of visual information for the SVV perception in case of bilateral vestibular loss.

We suggest that in patients with Usher type I, who have congenital complete bilateral vestibular loss, a very efficient reweighting of sensory information is installed since birth which could explain such similarity of the SVV performance between patients with Usher (type I and type II).

4.3. *SVV perception was independent to the two inclinations (clockwise and counter-clock-wise)*

The present study reported a similar SVV perception for the two inclinations (clockwise versus counter-clockwise) both in Usher's patients as well as in healthy participants. This finding is in line with previous studies showing no difference between the two tilt inclinations in adult participants (healthy as well as with bilateral vestibular deficiencies) [18]. Indeed, difference in SVV perception between the two tilt inclinations is observed in patients with unilateral vestibular deficiencies [3].

5. Conclusion

In the present study we showed that verticality perception is very variable in patients with Usher, most likely due to their visual impairment. The small impact of symmetrical vestibular loss on SVV in patients with Usher type I could be due to an efficient static compensation with a reweighting of sensory information (visual and proprioceptive).

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Funding

LIGHT4DEAF (ANR-15-RHUS-0001)

Author contribution

Conceptualization: MPB, SWV

Selection of patients: IA

Postural measure and data analysis: BM, SC and MPB

Writing original draft: BM, SC, AM, MPB and SWV.

Review and editing: IA, TVA

Acknowledgments

The authors thank the patients who participated in the study and Sidney Wiener for his helpful comments and revisions.

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