

# The Vestibulo-ocular Reflex During Active Head Motion in Chiari II Malformation

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**ABSTRACT: Background:** Chiari type II malformation (CII) is a developmental anomaly of the cerebellum and brainstem, which are important structures for processing the vestibulo-ocular reflex (VOR). We investigated the effects of the deformity of CII on the angular VOR during active head motion. **Methods:** Eye and head movements were recorded using an infrared eye tracker and magnetic head tracker in 20 participants with CII [11 males, age range 8-19 years, mean (SD) 14.4 (3.2) years]. Thirty-eight age-matched healthy children and adolescents (21 males) constituted the control group. Participants were instructed to 'look' in darkness at the position of their thumb, placed 25 cm away, while they made horizontal and vertical sinusoidal head rotations at frequencies of about 0.5 Hz and 2 Hz. Parametric and non-parametric tests were used to compare the two groups. **Results:** The VOR gains, the ratio of eye to head velocities, were abnormally low in two participants with CII and abnormally high in one participant with CII. **Conclusion:** The majority of participants with CII had normal VOR performance in this investigation. However, the deformity of CII can impair the active angular VOR in some patients with CII. Low gain is attributed to brainstem damage and high gain to cerebellar dysfunction.

**RÉSUMÉ: Le réflexe vestibulo-oculaire pendant les mouvements actifs de la tête dans la malformation de Chiari de type II.** *Contexte :* La malformation de Chiari de type II (CII) est une anomalie du développement du cervelet et du tronc cérébral, deux structures importantes pour l'intégrité du réflexe vestibulo-oculaire (RVO). Nous avons étudié les effets de la malformation CII sur le RVO angulaire pendant les mouvements actifs de la tête. *Méthodes :* Les mouvements des yeux et de la tête ont été enregistrés au moyen d'un écartomètre infra rouge et d'un écartomètre magnétique de la tête chez 20 participants atteints de CII, 11 garçons et 9 filles âgés de 8 à 19 ans (âge moyen 14,4 ans ; ÉT 3,2 ans). Le groupe témoin était composé de trente-huit enfants et adolescents en bonne santé, appariés pour l'âge (21 garçons et 17 filles). Les participants devaient fixer la position de leur pouce dans l'obscurité à une distance de 25 cm, pendant qu'ils faisaient des rotations sinusoidales horizontales et verticales de la tête à des fréquences d'à peu près 0,5 Hz et 2 Hz. Des tests paramétriques et non paramétriques ont été utilisés pour comparer les deux groupes. *Résultats :* Les gains du RVO, le rapport de la vitesse des yeux à la vitesse de la tête, étaient anormalement bas chez deux sujets atteints de CII et anormalement élevés chez un sujet atteint de CII. *Conclusion :* La majorité des participants atteints de CII avaient un fonctionnement normal du ROV dans cette étude. Cependant, la malformation de CII peut altérer le ROV angulaire actif chez certains patients. Un gain bas est attribué à l'atteinte du tronc cérébral et un gain élevé à la dysfonction cérébelleuse.

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Chiari type II malformation (CII) is a congenital deformity of the hindbrain associated with spina bifida. The hindbrain is distorted and caudally displaced in CII resulting in its herniation through foramen magnum. Hydrocephalus occurs commonly in patients with CII and usually requires shunt diversion.<sup>1</sup>

The vestibulo-ocular reflex (VOR) stabilizes images on the retina during head movements in order to maintain clear vision.<sup>2</sup> During head movements, the VOR generates smooth eye movements that approximate the magnitude of head movements in the opposite direction. The direct VOR arc involves the vestibular nerve, its nuclei, and their projections to the ocular motor nuclei.<sup>2</sup> The cerebellum can modulate the VOR through its connection with the vestibular nuclei.<sup>2</sup>

The effect of the deformity of CII on VOR has not been studied systematically. We investigated angular VOR gains in 20 children and adolescents with CII and compared the results with

those of 38 healthy children and adolescents. We hypothesized that the deformity of CII, through its effects on hindbrain structures, would impair the performance of the VOR. We also hypothesized that the VOR performance will be worse in participants with upper spinal lesion level, more shunt revisions,

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and nystagmus because these factors may be associated with worse prognosis.

## METHOD

### Participants

Twenty-three participants with myelomeningocele and CII were selected randomly from a cohort of participants in a spina bifida project funded by the National Institute of Child Health and Human Development. Inclusion criteria were an age range between 8 and 19 years, best corrected monocular visual acuity of at least 20/40, early shunted hydrocephalus, and a verbal or performance IQ of 70 or above, so that no participant had mental retardation.

Exclusion criteria were visual field defect on confrontation testing, paralytic strabismus, nystagmus on clinical examination within the range of eye movements recorded, medication with drugs that might interfere with eye movements (e.g., sedatives or anticonvulsant medication), and ocular, otological, psychiatric or neurological disorders unrelated to CII.

One person did not want to participate, another person was not available over the time we conducted the experiment, and one participant did not complete the task. Twenty of the remaining eligible participants with CII (11 males) completed the task. Their mean age (SD) was 14.4 (3.2) years. Seven had glasses (four were myopic and three were hyperopic). Ten had strabismus. Eleven were taking oxybutynin to control bladder symptoms associated with the myelomeningocele. Four of those eleven participants were also taking nitrofurantoin or Septra for urinary tract infection prophylaxis, and one was taking domperidone and omeprazole. None of these drugs are known to influence the VOR performance.

Forty age-matched normal children and adolescents in the control group were recruited by local advertising. One participant did not complete the task and another person did not show up on the day of the experiment. Thirty-eight of the remaining eligible healthy participants (21 males) completed the task. Their mean age (SD) was 13.8 (3.4) years. Fourteen were myopic (13 had glasses, one had contact lens) and one was hyperopic and rarely wore glasses. Three had strabismus. The eligibility of each participant to enter the study was confirmed by full clinical history, followed by neuro-ophthalmological and neurological examinations.

Ethical approval for this project was obtained from the Research Ethics Boards at the Hospital for Sick Children and the University Health Network. The study was in accord with the declaration of Helsinki guidelines. Written consent was obtained from participants or their legal guardian.

Power calculations were based on means and standard deviations of a visually guided upper limb pursuit task for spina bifida and control groups, using a two-sample t-test power analysis.<sup>3,4</sup> A sample size of 52 participants (26 per group) would detect significant difference in VOR gain between the CII and control groups with 80% power ( $1-\beta$ ), and 5% level of confidence ( $\alpha$ ). Unequal numbers of participants in each group changed the power of the study to ~82%.<sup>4</sup>

Spina bifida level was determined from physical examination. Based on the developmental process of neural tube closure,<sup>5</sup> two groups were distinguished: Lower (L1 and below, N=14) and upper (T12 and above, N=6) spinal lesion groups.

The number of shunt revisions in participants with CII was used as a surrogate marker for the cumulative effects of severely raised intracranial pressure.<sup>6</sup> Three shunt groups were created as described elsewhere.<sup>7</sup> Group one had one shunt and no shunt revisions (N=4), group two had one shunt revision (N=9), and group three had two or more shunt revisions (N=7).

Participants who had nystagmus on clinical examination within the range of the recorded eye movement tasks were excluded. Eight participants had clinically evident gaze-evoked nystagmus outside the range of the recorded eye movement tasks and in seven of these participants, a small amplitude ( $< 2^\circ$ ) and mostly horizontal nystagmus was evident only on eye movement recording.

### Equipment and procedures

We used an infrared, video eye tracking system (El-Mar Inc., Downsview, ON, Canada) to record eye position.<sup>8,9</sup> The system accuracy is  $0.5^\circ$  and its sampling frequency is 120 Hz. Head movements were recorded using a magnetic head tracker (Flock of Birds™, Ascension Technology Corp., Burlington, VT) as described previously.<sup>8,9</sup> Spectacles were not worn for at least one hour prior to testing and throughout the tasks. The uncorrected visual acuity was adequate for seeing and responding to the stimuli during calibration. Participants' alertness and performance were monitored.<sup>9</sup>

**Task.** Movements of the preferred eye in response to head rotations were measured in total darkness. During a training session, participants were instructed to look at an earth-fixed target located 57 cm away and perform active sinusoidal ( $\sim \pm 10^\circ$  amplitude) head on body rotations, in yaw (left-right) and pitch (up-down) at approximately 0.5 Hz and 2 Hz frequencies (Figure 1) cued by the sound of a metronome. Participants were then instructed to fixate an imaginary target 57 cm away in the dark. This proved to be difficult in a pilot study; therefore, at the beginning of the task participants were asked to look at their thumb nail bed, placed 25 cm in front of their viewing eye during the tasks, and remember its location when the laboratory lights were turned off. The 0.5 Hz head rotations were performed for ~40s while the 2 Hz head rotations were performed for ~20s for each direction as described elsewhere.<sup>9</sup>

### Processing of eye movement data

Head and eye movements were digitized for off-line analysis. Eye position traces were created after removing saccades and artifacts.<sup>9</sup> Head and eye position traces were then differentiated,<sup>9,10</sup> and each cycle of the resultant eye velocity trace was fitted with a sinusoidal function, using the least squares harmonic analysis method.<sup>11</sup> The VOR gain, a measure of the efficiency of the VOR system, for each cycle was calculated as the ratio of the amplitudes of the fitted sine function of the eye velocity to that of the head velocity.<sup>9</sup>

### Analyses

Mean VOR gain and SD were calculated for each participant. Analyses were performed using a Statistical Package for Social Sciences (SPSS Inc., Chicago, IL 2001). Normality of data distribution was tested.<sup>4</sup> Vestibulo-ocular reflex gains were compared between the control and CII groups using parametric

and non-parametric tests. Data from each participant with CII were analyzed further, as follows: Each participant in the CII group was classified as having abnormal VOR performance when their mean VOR gain lay outside the control group's mean  $\pm 2$  SD.

The VOR gains were correlated with age and number of shunt revisions using Spearman's test.<sup>4</sup> Shunt groups, spinal lesion level, and nystagmus were investigated using one-way analysis of variance (ANOVA) or Kruskal-Wallis test.<sup>4</sup> Significance was defined by *p* values  $\leq 0.05$ .

## RESULTS

The frequencies of head rotations were not normally distributed and their median value was significantly lower in participants with CII than in participants in the control group at 2 Hz head rotations (Table 1). However, there was no correlation between VOR gains and the frequencies of the rapid head rotations in either group. In addition, the peak head velocities were similar in both groups (Table 1).

Vestibulo-ocular reflex gains were normally distributed in the control group. The VOR gains in CII group were skewed. The median horizontal VOR gain in the CII group was significantly lower than the median gain in the control group at 2 Hz yaw head rotations. There were no significant differences in gains between the two groups at 0.5 Hz frequency or in pitch (Table 1). When individual comparisons against the control group were made, two CII participants had abnormally low horizontal (Figure 1A) and vertical gains and one CII participant had abnormally high horizontal gains (Figure 1B) and low vertical gains (Table 2). Two of the three participants with CII and impaired VOR gain

were not taking any medication and one was taking oxybutynin. The other 10 participants with CII who were taking oxybutynin had normal VOR gains.

The VOR gains did not correlate with age in either group. No significant differences in gains occurred between the upper and lower spinal lesion level groups, except for the horizontal VOR gain, which was significantly lower in the lower spinal lesion group (Figure 2A). There was no correlation between gains and the number of shunt revisions or shunt revision groups ( $p \geq 0.1$  for the various tasks). No significant difference in gains was found based on the presence of nystagmus (Figure 2B).

## DISCUSSION

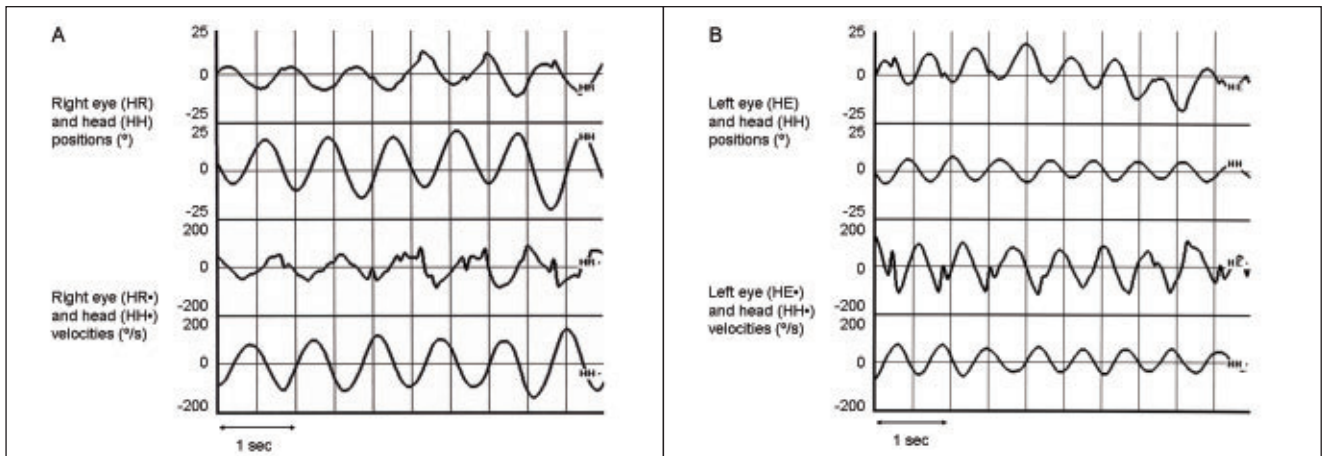
The angular VOR functions optimally during head rotation frequencies above 1 Hz. Vestibulo-ocular reflex gains do not vary with active head rotation frequencies between 1 to 2 Hz,<sup>12</sup> as was also illustrated by our results. Therefore, the small statistical difference in the median frequencies of head rotations between the two groups at 2 Hz is not considered important clinically. Furthermore, all participants generated similar peak head velocities and adequate head rotation frequencies to assess a wide range of VOR performance.

Two participants with CII had subnormal gains. This lowered the median horizontal VOR gain significantly in the CII group at 2 Hz head rotations in comparison to the control group. The neural circuits processing the VOR appear to be functioning subnormally in some individuals with CII. Brainstem dysfunction has been documented in infants with CII using brainstem auditory evoked potentials.<sup>13</sup> Brainstem disease may lower VOR gains.<sup>2</sup> Only one participant with CII had high gains. The VOR

**Table 1: VOR characteristics in the control and Chiari type II malformation groups**

	Control group	Chiari II group	<i>p</i> value
<b>Horizontal</b>			
VOR gain at 0.5 Hz	1.07 [0.82-1.47]	1.07 [0.46-1.43]	0.74
Head rotation frequency	0.5 [0.33-0.77]	0.5 [0.29-0.58]	0.98
Peak head velocity	21.4 [12.1-38.2]	24.9 [13-38.8]	0.14
VOR gain at 2 Hz	1.12 [0.76-1.71]	1.05 [0.5-1.61]	0.03*
Head rotation frequency	2.15 [1.1-4.37]	1.64 [0.77-3.32]	0.01*
Peak head velocity	75.1 [43.7-146.7]	78.3 [46.8-145.6]	0.84
<b>Vertical</b>			
VOR gain at 0.5 Hz	0.94 [0.57-1.36]	0.94 [0.5-1.35]	0.50
Head rotation frequency	0.51 [0.47-0.58]	0.5 [0.39-0.58]	0.53
Peak head velocity	22.4 [12.2-38.1]	25.9 [11-54.8]	0.18
VOR gain at 2 Hz	1.03 [0.75-1.42]	1.1 [0.5-1.37]	0.79
Head rotation frequency	2.28 [1.44-4.09]	1.84 [1.25-3.32]	0.03*
Peak head velocity	66.6 [34.7-105.2]	58.3 [32.7-125.4]	0.86

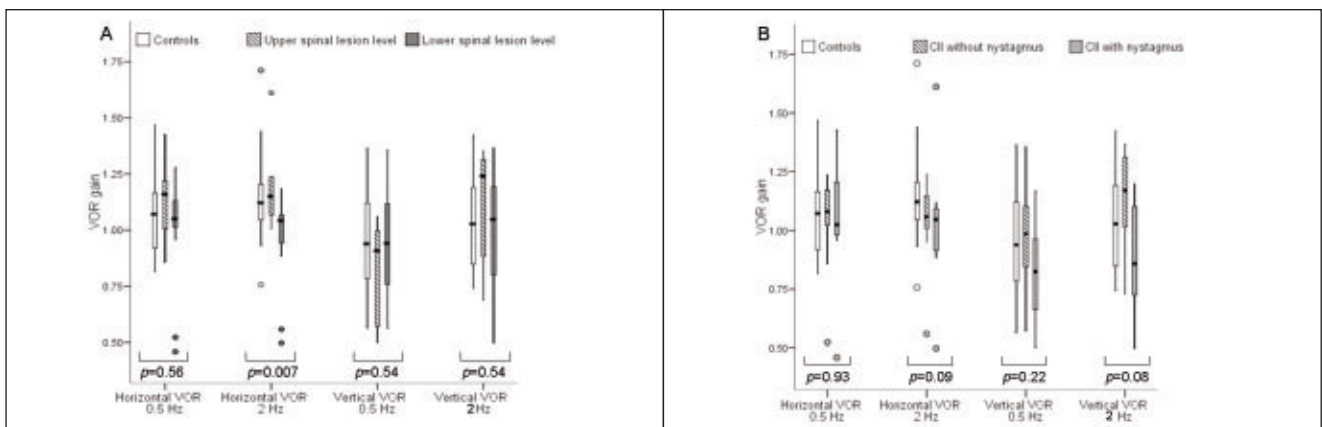
Median angular VOR gains, median frequencies of head rotation in Hz, and median peak head velocities in % [range] are illustrated



**Figure 1:** Graphs of the active horizontal angular VOR in two participants with CII. Horizontal right eye (HR), left eye (HE) and head (HH) position traces are shown in the upper two traces of the figures in response to sinusoidal head rotation in A) a 13-year-old girl with low VOR gain and in B) a 17-year-old girl with high VOR gain. Upward deflection represents rightward motion, and downward is leftward motion. The corresponding eye and head velocity traces are shown in the lower two traces of the Figures. In (A), the amplitude of the eye velocity trace is smaller than the amplitude of the head velocity trace. Mean VOR gain at about 1.3 Hz head rotations was low (0.56) for this participant. While in (B), the amplitude of the eye velocity trace is larger than the amplitude of the head velocity trace. Mean VOR gain at about 1.7 Hz head rotations was high (1.61) for this participant.

gains may be either normal or high in cerebellar disease.<sup>2</sup> Damage to Purkinje cell projections from the flocculus and paraflocculus, which inhibit the vestibular nuclei, may explain elevated VOR gains. The deformity of CII affects both the brainstem and cerebellum to varying degrees,<sup>1</sup> which can explain the abnormal VOR gains that we recorded in some participants with CII. No prior study similar to ours is reported; although three people aged 4, 22, and 44 years with CII were reported to have ‘impaired VOR gains’; quantitative details of their VOR performance were not provided.<sup>14</sup>

Nystagmus was not a correlate of an abnormal VOR, since many participants with nystagmus had normal VOR gains. The absence of nystagmus does not predict normal VOR gains since one participant who did not have nystagmus, had low VOR gain. Studies of spinal lesion level have shown that upper spinal lesions are associated with more brain anomalies.<sup>15</sup> However, participants with upper spinal lesion level did not have more abnormal VOR gains as a group. The cumulative effects of raised intracranial pressure, inferred from the number of shunt revisions, had no adverse effects on VOR circuits in CII.



**Figure 2:** Box plots showing the median, interquartile range, and extreme values of the VOR gain at two head rotation frequencies and directions in the control and CII groups based on (A) spinal lesion level and (B) nystagmus. The horizontal VOR gains at 2 Hz head rotations in the CII participants with lower spinal lesion level (n=14) were significantly lower than gains in the control group (n=38) and CII participants with upper spinal lesion level (n=6). VOR gains did not differ significantly among participants in the control group (n=38), CII participants without nystagmus (n=12) or CII participants with nystagmus (n=8).

**Table 2: Participants with Chiari II abnormal VOR gains**

Participant	Nystagmus	Spinal lesion level	Horizontal gain at ~0.5 Hz	Horizontal gain at ~2 Hz	Vertical gain at ~0.5 Hz	Vertical gain at ~2 Hz
1	+	T 10	1.43	1.61	0.5	0.69
2	-	L1	0.52	0.56	0.63	0.8
3	+	L3	0.46	0.5	0.57	0.5

The habitual use of corrective spectacles affects VOR gain. Myopes tend to have lower gains and hyperopes higher gains.<sup>16</sup> Two of three participants with CII and abnormal VOR gains wore spectacles. One participant had spectacles for myopia. Her horizontal VOR gains were high, while the other had spectacles for hyperopia. His horizontal VOR gains were low. Therefore, any spectacle influence on VOR gains would not explain their abnormal VOR gains, because the anticipated effect of wearing spectacles on VOR gains is opposite to their VOR gains abnormalities.<sup>16</sup> Additionally, many participants did not wear their spectacles habitually and were instructed not to wear their spectacles for at least one hour prior to testing to remove any effect of adaptation to corrective lens on VOR gain.<sup>17</sup>

Vestibulo-ocular reflex gains were mostly above unity in both groups in our study, reflecting the influence of near viewing.<sup>9,18</sup> The VOR gains are also higher during active head rotations than during passive whole body rotations.<sup>12</sup> The VOR gains may have also been enhanced in all participants from the proprioceptive input of the participants' thumbs, which they attempted to fixate in total darkness. The effect of proprioceptive input from the limbs on VOR gain has not been investigated systematically but its effects on the active VOR appear to be weak.<sup>19</sup> We instructed our participants to attempt viewing a nearer target (their thumb) in darkness because they found it difficult to maintain fixation of a more distant imaginary target.

The cervico-ocular reflex (COR) might aid gaze stabilization but its gain is negligible in healthy humans.<sup>2</sup> The COR gain is enhanced in patients with bilateral vestibular disease.<sup>20</sup> This compensatory COR enhancement is modest and is best seen at low velocity (< 10°/s) and low frequency (< 0.2 Hz) neck movements.<sup>20</sup> It is negligible for mid-to-high frequency neck rotations,<sup>20</sup> and therefore unlikely to have any measurable influence on our results.

We conclude that many patients with CII typically have a normal active angular VOR. The function of the neural circuits involved in processing the VOR are mostly normal in CII, perhaps because of the chronic developmental nature of this congenital deformity, or because there is adequate neural reserve despite the anatomical abnormalities of the hindbrain. Alternatively, the structures involved in processing the VOR may only be anatomically but not functionally affected by this deformity. However, CII can be associated with impaired VOR performance. Low VOR gain is attributed to brainstem damage and high VOR gain to cerebellar dysfunction. Abnormal VOR gain may cause oscillopsia or visual blurring during rapid head

motion. We did not measure the effects of the abnormal gain we detected on visual function, or establish the effects of visual fixation on enhancing the VOR when viewing a stationary image or suppressing the VOR when tracking a moving object.

It will be informative to investigate VOR adaptation, which provides a method for studying ocular motor learning, in patients with CII. Such a study could provide an opportunity to investigate the effects of the CII deformity on the flocculus and paraflocculus, which participate in adaptation of the VOR to altered visual or vestibular information.<sup>2</sup>

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