Smooth ocular pursuit in Chiari type II malformation

Michael S Salman* MRCP PhD, Section of Paediatric Neurology, Children's Hospital, University of Manitoba, Winnipeg, Manitoba;
James A Sharpe MD FRCPC, Division of Neurology;
Linda Lillakas BA;
Martin J Steinbach PhD, Vision Science Research Program, University Health Network, Toronto;
Maureen Dennis PhD, Division of Psychology, The Hospital for Sick Children, University Health Network, University of Toronto, Toronto, Ontario, Canada.

**Correspondence to first author at* Section of Paediatric Neurology, AE 108, Children's Hospital, 820 Sherbrook St, Winnipeg, Manitoba R3A 1R9, Canada.
E-mail: msalman@hsc.mb.ca

Chiari type II malformation (CII) is a congenital anomaly of the cerebellum and brainstem, both important structures for processing smooth ocular pursuit. CII is associated with myelomeningocele and hydrocephalus. We investigated the effects of CII on smooth pursuit (SP) eye movements, and determined the effects of spinal lesion level, number of shunt revisions, nystagmus, and brain dysmorphology on SP. SP was recorded using an infrared eye tracker in 21 participants with CII (11 males, 10 females; age range 8–19y, mean 14y 3mo [SD 3y 2mo]). Thirty-eight healthy children (21 males, 17 females) constituted the comparison group. Participants followed a visual target moving sinusoidally at ±10° amplitude, horizontally and vertically at 0.25 or 0.5Hz. SP gains, the ratio of eye to target velocities, were abnormal in the CII group with nystagmus (n=8). The number of shunt revisions (range 0–10), brain dysmorphology, or spinal lesion level (n=15 for lower and n=6 for upper spinal lesion level) did not correlate with SP gains. SP is impaired in children with CII and nystagmus. Abnormal pursuit might be related to the CII dysgenesis or to effects of hydrocephalus. The lack of effect of shunt revisions and abnormal tracking in participants with nystagmus provide evidence that it is related primarily to the cerebellar and brainstem malformation.

Smooth ocular pursuit consists of slow conjugate eye movements that stabilize the image of a moving target on or near the fovea to ensure optimal visual acuity. Smooth pursuit (SP) is usually generated in response to a moving small visual stimulus.[1] Neural processing of SP involves the frontal,[2] temporal, and parietal lobes,[3] the brainstem tegmentum, and the cerebellum.[4-6]

Chiari type II malformation (CII) is a congenital deformity of the brainstem and cerebellum that is associated with myelomeningocele. In CII, the posterior fossa is small and, as a result, its contents are distorted as they herniate through the tentorial incisura and the foramen magnum.[7] Hydrocephalus requiring shunt diversion occurs in more than 85% of patients with myelomeningocele.[7]

Recordings of smooth ocular pursuit in children with CII are lacking. Analysis of SP in children with CII is potentially interesting because it can provide insight about whether the congenital deformity of CII, which involves neural structures that process SP, can affect the ability to develop normal SP eye movements during childhood. In this study, we hypothesized that SP would be adversely affected by the deformity of CII, and that SP impairment in CII would be worse in participants with upper spinal lesion level because they usually have a more dysmorphic brain on magnetic resonance imaging (MRI),[8] multiple shunt revisions, which signify more damage from raised intracranial pressure, and gaze-evoked nystagmus, which disrupts smooth eye movements. We also postulated that impairment of SP would correlate with the deformity of the cerebellar vermis.

Method

PARTICIPANTS

Twenty-three participants with myelomeningocele and CII were selected randomly from a cohort of children who were participants in a spina bifida project funded by the National Institute of Child Health and Human Development (USA). Forty typically developing children in the comparison group were recruited by local advertising. Participants were between 8 and 19 years of age. All had best corrected near and distant monocular visual acuity of at least 20/40. None had mental retardation.* Exclusion criteria were nystagmus on clinical examination within the range of the eye movement task, medication with drugs that might interfere with eye movements, acute hydrocephalus, ocular or neurological disorders unrelated to CII, and syringobulbia on MRI. Saccades in these participants have been investigated previously.[9]

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

Means and standard deviations (SDs) for myelomeningocele and comparison groups on a visually-guided upper limb pursuit task,[10] were used to guide power calculations.[9,11] Based on a two-sample t-test power analysis, a sample size of 26 per group would detect a significant difference between the CII and comparison groups with 80% power, and 5% confidence level.[11] Unequal numbers of participants in each group and a larger sample size changed the power to 82%.[11]

See end of paper for list of abbreviations.

*UK usage: learning disability.

Spinal lesion level

Two groups were distinguished: upper spinal lesion level group (thoracic vertebrae 12 and above, $n=6$), and lower spinal lesion level group (lumbar vertebrae 1 and below, $n=15$).[9] This is based on the developmental process of neural tube closure.[12]

Hydrocephalus

Three shunt groups were created. Group 1 had no shunt revisions, group 2 had one shunt revision, and group 3 had two or more shunt revisions.

Nystagmus

Participants who had nystagmus on clinical examination within the range of the eye movement tasks were excluded. Eight participants had nystagmus that was clinically apparent *only* in eccentric gaze and, in seven of these participants, we found low amplitude (<2°) and predominantly horizontal, gaze-evoked nystagmus on eye movement recording.

MRI measurements

Nineteen participants with CII had artifact-free brain MRI. Computer software (Ataman Software Inc, 1998) calculated distances or areas of the selected regions of interest on a T_1- or T_2-weighted midsagittal MRI. The following were measured: the longest longitudinal and transverse distances across the vermis, herniation distance, and area below foramen magnum, intracranial fossa, posterior fossa, cerebellar vermis, vermis lobules I to V, and vermis lobules VI to VII areas. All of these measurements are significantly different in children with CII in comparison to typically developing children.[13]

EQUIPMENT AND PROCEDURES

An infrared, video eye tracking system (El-Mar Inc, Downsview, ON, Canada) was used to record horizontal and vertical eye position.[14] The video image was sampled at 120Hz. The system's accuracy was 0.5°. The experimental set-up has been discussed in detail before,[15] but briefly, each participant was seated on a chair facing the center of a computer monitor located 57cm from the participant's cornea. A chin rest was used to stabilize the participant's head. The visual target was a 2mm, white square light. Eye movement positions were calibrated for each eye at 14 fixation light points.

Participants' performance and alertness were monitored by a video camera and by an oscilloscope display of eye movements to provide feedback during the task.

Task

A monocular viewing condition was used. The non-preferred eye was covered. Movements of the viewing eye were measured. The target movement was smooth and sinusoidal (Fig. 1), with ±10° amplitude horizontally and vertically at 0.25 and 0.5Hz, yielding peak target velocities of 15.5°/s and 31°/s respectively, and is discussed in more detail elsewhere.[15]

Data processing

This has been described in detail in a previous paper,[15] but briefly, target and eye movements were digitized for offline analysis. Saccades were automatically marked by purpose-designed computer software. Eye position traces were created after removing saccades and artifacts, and replacing the missing parts with an interpolated parabola as described elsewhere.[15] Target and eye position traces were then differentiated[16] to obtain velocity traces. Each cycle of the resultant eye velocity trace was then fitted with a sinusoidal function to determine the amplitude and phase of the response for a given frequency.[17] SP gain for each cycle was calculated as the ratio of the amplitude of the eye velocity trace to the amplitude of the target velocity trace, while SP phase was the difference in the angles of the sine function of the eye and target velocity traces.[15]

ANALYSES

For each participant, the means and SDs of SP gains and phases at each target direction and frequency were computed. Analyses were performed using a Statistical Package for Social Sciences for Windows 2001 (SPSS Inc. Chicago, IL, USA). Normality of data distribution was tested using the mean, median, SD, skewness, kurtosis, and box plots.[11]

SP parameters were compared between the comparison and CII groups and within the CII group based on spinal lesion level and nystagmus using independent student *t*-tests for normally distributed data or the Mann–Whitney *U* test for non-parametric data.[11] SP parameters were correlated

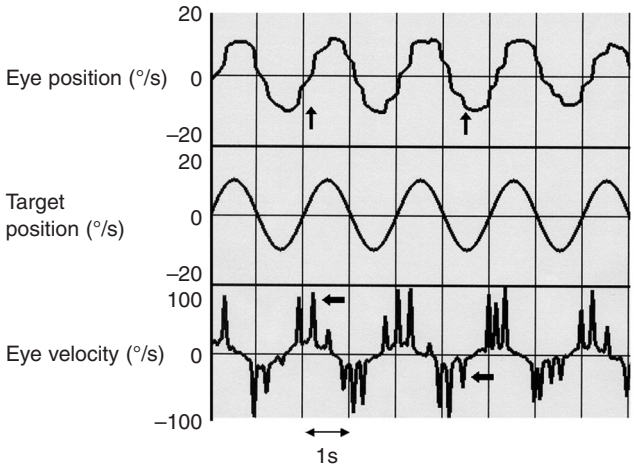

Figure 1: *Horizontal smooth pursuit (SP) of right eye (upper trace) in a child with Chiari type II malformation and nystagmus in response to a visual target (middle trace) moving sinusoidally at 0.5Hz. Upward deflection represents rightward movement. Upper trace shows fast eye movements, which represent catch-up saccades (vertical arrows). Corresponding eye velocity (bottom trace) shows multiple deflections (horizontal arrows) that correspond to catch-up saccades. SP gain was low (0.39). Gain was calculated after removing these saccades.*

with age, the number of shunt revisions, and MRI measurements using the Spearman's test.[11] Shunt groups were investigated using one-way analysis of variance for normally distributed data or Kruskal–Wallis test for non-parametric data. Bonferroni correction was applied because multiple comparisons were made.[11] Significance was defined by $p<0.01$.

Results

Demographics of the participants are shown in Table I. One child with CII declined to participate and another child with CII was not available over the time we conducted the experiment. One child in the comparison group did not complete the task and another child in the comparison group did not attend on the day of the experiment. Fifty-nine of the remaining eligible participants consented and completed the task. SP gains but not phases in the two groups had approximately normal distributions. SP gains within the CII subgroups based on spinal lesion level and nystagmus had a skewed distribution.

Mean SP gains, and the ratios of eye velocities to target velocities, were lower in the CII group with nystagmus ($n=8$) compared with the CII group who did not have nystagmus ($n=13$) or the comparison group ($n=38$; Table II, Fig. 2). For example, mean (median) horizontal gain at 0.25Hz target frequency was 0.54 (0.5) in the CII group with nystagmus, 0.85 (0.82) in the CII group without nystagmus, and 0.84 (0.87) in the comparison group. The differences were significant for horizontal but not vertical SP gains (Fig. 2).

SP phases were not significantly different between the CII and comparison groups (Table II). In the CII group, neither SP mean gains nor phases differed significantly between participants with upper compared with lower spinal lesion level (p values ranged from 0.53 to 0.91 depending on target frequency and direction). Moreover, there was no correlation between SP gains or phases, and the number of shunt revisions (p values ranged from 0.15 to 0.95 depending on the task). There was no significant correlation between SP gains and MRI measurements when the effect of nystagmus was taken into account (Spearman's rank correlation coefficient ranged from 0.54, $p=0.03$ [for correlation between vertical SP gain at 0.25Hz and vermis lobules VI and VII area] to 0.004, $p=0.99$ depending on the task and the MRI parameter).

Discussion

SP gains, a measure of the efficiency of the SP system, were

Table I: Demographic information of comparison and Chiari type II malformation (CII) groups

	Comparison group	*CII group*
Number of participants	38	21
Sex, M:F	21:17	11:10
Mean age (SD), y:m	13:10 (3:5)	14:3 (3:2)
Strabismus	3	10
Shunted hydrocephalus	0	21 (5 had one shunt with no revisions, 9 had 1 shunt revision, 7 had 2 or more shunt revisions)
Nystagmus[a]	0	8
Ambulatory	38	9

[a]Nystagmus present on clinical examination but not in range of eye movement tasks. In seven of eight participants, a sub-clinical small amplitude nystagmus was also noted on eye movement recordings.

Table II: Smooth pursuit (SP) characteristics in comparison and Chiari type II malformation (CII) groups[a]

	Comparison group	*CII group*	*Mean difference*	*p value*
Horizontal SP at 0.25Hz				
Mean no. of cycles	15.2 (14.2–16.3)	15 (13.8–16.1)	0.2 (–1.4 to 1.9)	0.75
Mean gain	0.84 (0.78–0.9)	0.73 (0.64–0.82)	0.11 (0.01–0.21)	0.038
Median phase	–6.5 [–11.2 to 4.7]	–5.5 [–11.6 to 42.2]	NA	0.346
Horizontal SP at 0.5Hz				
Mean no. of cycles	14.1 (12.8–15.3)	13.6 (12–15.2)	0.5 (–1.5 to 2.4)	0.63
Mean gain	0.73 (0.66–0.80)	0.52 (0.41–0.63)	0.21 (0.09–0.34)	0.001
Median phase	–15.5 [–30.5 to –4]	–18.4 [–28.8 to 27.9]	NA	0.359
Vertical SP at 0.25Hz				
Mean no. of cycles	13.5 (12.5–14.5)	12.9 (11.2–14.6)	0.6 (–1.2 to 2.4)	0.5
Mean gain	0.68 (0.6–0.76)	0.55 (0.48–0.63)	0.13 (0.01–0.24)	0.016
Median phase	–3.5 [–18.3 to 10.9]	–3.7 [–11.5 to 22.5]	NA	0.728
Vertical SP at 0.5Hz				
Mean no. of cycles	11 (9.9–12)	11.4 (10.2–12.7)	–0.4 (–2.1 to 1.2)	0.56
Mean gain	0.45 (0.39–0.52)	0.4 (0.34–0.45)	0.05 (–0.04 to 0.15)	0.203
Median phase	–9.5 [–30.3 to 16.2]	–13 [–38 to 28.8]	NA	0.975

[a]Means values (95% confidence interval of the mean or mean difference) are shown except for SP phases where median values are shown in degrees [range]. SP phases were not normally distributed hence mean difference is not applicable (NA). Negative phase indicates a lag of eyes behind target speed.

found to be subnormal in children with CII and nystagmus, but normal in children with CII who did not have nystagmus. One study[18] reported saccadic horizontal SP using video recording in 10 of 28 participants, aged 4 to 34 years with Chiari malformation. Saccadic SP indicates subnormal SP gain. Seventeen participants in that study had horizontal nystagmus.[18] Saccadic SP has also been described in a number of case reports of Chiari malformations.[19,20] These studies had a small number of participants, were not controlled, did not record eye movements, or use electro-oculography.

The reduced SP gains identified in this investigation could reflect dysfunction of any of several structures involved in SP processing. The deformity of CII involves the brainstem and cerebellum, both important structures in SP processing.[1,4-6] Although all participants had shunted hydrocephalus, which might also impair SP,[21] the number of shunt revisions, assumed to be a surrogate marker for the cumulative effects of severely raised intracranial pressure on the developing brain,[22] did not correlate with SP gains. Furthermore, children with CII who did not have nystagmus had normal SP, despite their shunted hydrocephalus. The results provide evidence that the malformation of the hindbrain, not the hydrocephalus, is responsible for the subnormal SP in CII. Gaze-evoked nystagmus was characteristic of the CII group with subnormal SP. This type of nystagmus is usually caused by deficits in the neural integrator, which is located in the brainstem (nucleus prepositus hypoglossi and the vestibular nuclei for horizontal eye movements) or through cerebellar floccular and paraflocculer lobe involvement.[23] These brain regions also participate in SP processing,[1,24] and their involvement by the deformity of CII can be expected to impair SP eye movements in addition to causing gaze-evoked nystagmus.

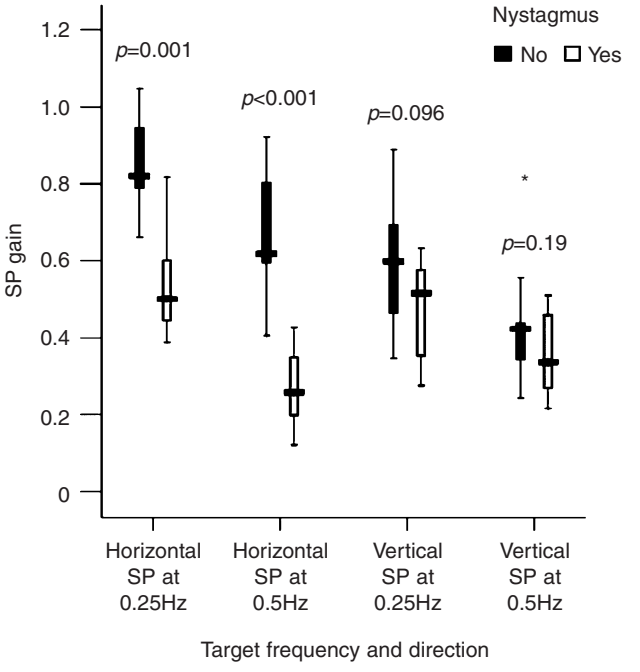

Figure 2: *Box plots showing the median, interquartile range, and an extreme value (*) for smooth pursuit (SP) gains in the Chiari type II (CII) groups based on the presence (n=8) and absence of nystagmus (n=13). Participants with CII and nystagmus had lower SP gains.*

Although vertical SP gain in children with CII and nystagmus was lower than SP gain in children with CII who did not have nystagmus, the difference did not reach statistical significance. This lack of significance may be due to one or more of several reasons. First, the gaze-evoked nystagmus was predominantly horizontal and this may make horizontal tracking more likely to be affected through involvement of the same network of neurons that process horizontal eye movements. Second, the deformity of CII may affect other structures in the brainstem and cerebellum that are predominantly responsible for processing horizontal SP tracking. Third, the current investigation may be inadequately powered to pick up smaller differences in vertical SP gains between the two groups. This smaller difference may have arisen because of the lower vertical SP gains in typically developing children in comparison to horizontal gains.[15]

SP was not adversely affected by upper spinal lesion level, known to be associated with more severe cognitive and limb movement disabilities, and with more cerebellar and midbrain anomalies.[8,22] This may be related to the relatively small number of participants with an upper spinal lesion level.

Structure-function correlation between brain MRI abnormalities in CII and SP are sparse.[25] Abnormalities in horizontal SP, as detected on video tape recordings, were also not related to qualitative central nervous system changes seen on MRI in 28 participants with Chiari malformation.[25] In CII, the vermis is compressed and its entire midsagittal surface area is enlarged.[13] This enlargement involves lobules VI and VII, which participate in SP processing.[5] The ability of the midsagittal vermis area to expand in all directions, because of its midline location,[13] is postulated to leave its ocular motor function intact. This proposition is supported by the current investigations' findings of the absence of any consistent correlation between SP gains and midsagittal vermis or lobules VI and VII areas. In addition, saccades, which are also processed in vermis lobules VI and VII, are normal in most participants with CII.[9] It is, therefore, likely that the impaired SP gain in children with CII and nystagmus is caused by floccular and paraflocculer lobe involvement.

Sinusoidal target movements are predictable. Phase lag is close to zero with predictable target movements and increases with increasing target frequency in adults.[3] SP phases were similar in the two groups, indicating that prediction in the SP system is resistant to the deformity of CII and the effects of hydrocephalus.

Recording eye movements in children has many challenges. The use of a non-invasive and well-tolerated eye tracker in a relatively large number of children with CII demonstrates its potential for investigation of brain dysfunction in children.

Accepted for publication 22nd October 2006.

Acknowledgments
We thank Dr M Eizenman, Mrs I Dror, and Mr A Blakeman for their support and we thank the participants and their families for their time.

Funding sources
KidsAction; Spina Bifida and Hydrocephalus Association of Canada; Clinician Scientist training program award, Vision Science Research Program at the University of Toronto; Bloorview MacMillan Hospital foundation grants (MS Salman); NIH grant 'Spina bifida: Cognitive

and neurobiological variability' (J Fletcher, M Dennis); CIHR of Canada Grants MT5404 and ME 5909 (JAS); and NSERC of Canada A7664, the Sir Jules Thorn Charitable Trust, and the Krembil Family Foundation Grants (MJS).

References

1. Leigh RJ, Zee DS. (1999) *The Neurology of Eye Movements.* New York: Oxford University Press. p 151–197.
2. Morrow MJ, Sharpe JA. (1995) Deficits of smooth pursuit eye movement after unilateral frontal lobe lesions. *Ann Neurol* **37:** 443–451.
3. Morrow MJ, Sharpe JA. (1990) Cerebral hemispheric localization of smooth pursuit asymmetry. *Neurology* **40:** 284–292.
4. Shinmei Y, Yamanobe T, Fukushima J, Fukushima K. (2002) Purkinje cells of the cerebellar dorsal vermis: simple-spike activity during pursuit and passive whole-body rotation. *J Neurophysiol* **87:** 1836–1849.
5. Takagi M, Zee DS, Tamargo RJ. (2000) Effects of lesions of the oculomotor cerebellar vermis on eye movements in primate: smooth pursuit. *J Neurophysiol* **83:** 2047–2062.
6. Thier P, Ilg UJ. (2005) The neural basis of smooth-pursuit eye movements. *Curr Opin Neurobiol* **15:** 645–652.
7. Gilbert JN, Jones KL, Rorke LB, Chernoff GF, James HE. (1986) Central nervous system anomalies associated with meningomyelocele, hydrocephalus, and the Arnold–Chiari malformation: reappraisal of theories regarding the pathogenesis of posterior neural tube closure defects. *Neurosurgery* **18:** 559–564.
8. Fletcher JM, Dennis M, Northrup H, Barnes MA, Hannay HJ, Landry SH, Copeland K, Blaser SE, Kramer LA, Brandt ME, Francis DJ. (2004) Spina bifida: genes, brain, and development. *Int Rev Res Ment Retard* **29:** 63–117.
9. Salman MS, Sharpe JA, Eizenman M, Lillakas L, To T, Westall C, Steinbach MJ, Dennis M. (2005) Saccades in children with Chiari type II malformation. *Neurology* **64:** 2098–2101.
10. Dennis M, Fletcher JM, Rogers T, Hetherington R, Francis DJ. (2002) Object-based and action-based visual perception in children with spina bifida and hydrocephalus. *J Int Neuropsychol Soc* **8:** 95–106.
11. Altman DG. (1995) *Practical Statistics for Medical Research.* London: Chapman and Hall.
12. Van Allen MI, Kalousek DK, Chernoff GF, Juriloff D, Harris M, McGillivray BC, Yong SL, Langlois S, MacLeod PM, Chitayat D, et al. (1993) Evidence for multi-site closure of the neural tube in humans. *Am J Med Genet* **47:** 723–743.
13. Salman MS, Blaser SE, Sharpe JA, Dennis M. (2006) Cerebellar vermis morphology in children with spina bifida and Chiari type II malformation. *Childs Nerv Syst* **22:** 385–393.
14. DiScenna AO, Das V, Zivotofsky AZ, Seidman SH, Leigh RJ. (1995) Evaluation of a video tracking device for measurement of horizontal and vertical eye rotations during locomotion. *J Neurosci Methods* **58:** 89–94.
15. Salman MS, Sharpe JA, Lillakas L, Dennis M, Steinbach MJ. (2006) Smooth pursuit eye movements in children. *Exp Brain Res* **169:** 139–143.
16. Selesnick IW. (2002) Maximally flat low-pass digital differentiators. *IEEE Trans on Circuits and Systems II.* **49:** 219–222.
17. Sokolnikoff IS, Sokolnikoff E. (1941) *Least Squares Harmonic Analysis. Higher Mathematics for Engineers and Physicists.* New York: McGraw-Hill. p 554–550.
18. Lennerstrand G, Gallo JE. (1990) Neuro-ophthalmological evaluation of patients with myelomeningocele and Chiari malformations. *Dev Med Child Neurol* **32:** 415–422.
19. Longridge NS, Mallinson AI. (1985) Arnold-Chiari malformation and the otolaryngologist: place of magnetic resonance imaging and electronystagmography. *Laryngoscope* **95:** 335–339.
20. Spooner JW, Baloh RW. (1981) Arnold-Chiari malformation: improvement in eye movements after surgical treatment. *Brain* **104:** 51–60.
21. Löppönen H, Sorri M, Serlo W, von Wendt L. (1992) ENG findings of shunt-treated hydrocephalus in children. *Int J Pediatr Otorhinolaryngol* **23:** 35–44.
22. Dennis M, Fitz CR, Netley CT, Sugar J, Harwood-Nash DC, Hendrick EB, Hoffman HJ, Humphreys RP. (1981) The intelligence of hydrocephalic children. *Arch Neurol* **38:** 607–615.
23. Zee DS, Yamazaki A, Butler PH, Gucer G. (1981) Effects of ablation of flocculus and paraflocculus on eye movements in primate. *J Neurophysiol* **46:** 878–899.
24. Leung HC, Suh M, Kettner RE. (2000) Cerebellar flocculus and paraflocculus Purkinje cell activity during circular pursuit in monkeys. *J Neurophysiol* **83:** 13–30.
25. Lennerstrand G, Gallo JE, Samuelsson L. (1990) Neuro-ophthalmological findings in relation to CNS lesions in patients with myelomeningocele. *Dev Med Child Neurol* **32:** 423–431.

List of abbreviations

CII	Chiari type II malformation
SP	Smooth pursuit