Saccades in children with Chiari type II malformation

8 authors, including:

Saccades in children with spina bifida and Chiari type II malformation

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Abstract—*Background:* Saccades are essential for optimal visual function. Chiari type II malformation (CII) is a congenital anomaly of the cerebellum and brainstem, associated with spina bifida. *Objective:* To investigate the effects of CII on saccades and correlate saccadic parameters with brain MRI measurements. *Methods:* Saccades were recorded in 21 participants with CII, aged 8 to 19, using an infrared eye tracker. Thirty-nine typically developing children served as controls. Participants made saccades to horizontal and vertical target steps. Nineteen participants with CII had MRI. Regression analyses were used to investigate the effects of spinal lesion level, number of shunt revisions, presence of nystagmus, and midsagittal MRI measurements on saccades. *Results:* Saccadic amplitude gains, asymptotic peak velocities, and latencies did not differ between the control and CII groups ($p > 0.01$). No significant differences were found between saccadic gains, asymptotic peak velocities or latencies, and spinal lesion level, number of shunt revisions, presence of nystagmus, or MRI measurements. *Conclusions:* Saccades were normal in most participants with Chiari II malformation (CII). Neural coding of saccades is robust and is typically not affected by the anatomic deformity of CII.

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Chiari type II malformation (CII) is a congenital deformity of the brainstem and cerebellum associated with spina bifida.[1] 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.[2] Hydrocephalus requiring shunt diversion occurs in >85% of patients with CII.[1,3,4]

Saccades are fast eye movements that are essential for optimal visual function.[5] The cerebellum plays an important role in the control of saccade accuracy, dynamics, and trajectory.[5,6] Ablation of vermis lobules VI and VII causes saccadic hypometria of ipsiversive saccades with increased latency.[7,8] Symmetric bilateral lesions in vermis lobules VI and VII cause bilateral horizontal hypometria and slight increase in latency. Lobules VI and VII in the posterior cerebellar vermis, together with the caudal part of the fastigial nucleus, play key roles in modulating the amplitude of each saccade,[5,9,10] because dysmetric saccades occur in humans with damage involving the cerebellum[11-14] and during temporary inactivation of the cerebellum by transcutaneous magnetic stimulation.[15] Functional MRI studies have shown increased blood flow during visually guided saccades in the cerebellar hemispheres, vermis, and cerebellar peduncles in healthy humans.[16,17]

Saccadic dysmetria has been reported in a few case studies of patients with CII.[18-23] Both hypo- and hypermetria were described either on clinical examination or in eye movements recorded using electrooculography. Other characteristics of saccades have not been described in CII.

The effects of CII deformity on the neuronal circuit involved in saccadic processing have not been studied systematically. In this investigation, we hypothesized that saccadic accuracy, peak velocity, and latency would be abnormal in children with CII and that saccade impairment in the CII group would be worse in participants with upper lesion spina bifida, multiple shunt revisions, nystagmus, and severe brain abnormalities on MRI.

Methods. Participants were selected from patients in a spina bifida project, funded by the National Institute of Child Health and Human Development. Twenty-one children with spina bifida myelomeningocele and CII with hydrocephalus, treated before age 3 months, were studied. Their age range was between 8 and 19 years. They had best corrected monocular visual acuity of at least 20/40 and a verbal or performance IQ of ≥70. Thirty-nine typically developing children served as controls and were recruited by local

Table 1 *Demographic information for control and Chiari type II malformation (CII) groups*

Parameter	Control group	CII group
No. of participants	39	21
Female	18	10
Age (SD), y	13.7 (3.5)	14.3 (3.2)
Strabismus	3	10*
Strabismus surgery	1	2
Past history of seizures	2	3
Shunted hydrocephalus	0	21*
No shunt revision		5
1 shunt revision		9
≥2 shunt revisions		7
Nystagmus†	0	8*
Ambulatory	39	9*

* $p \leq 0.001$ on χ^2 test.

† Nystagmus present on clinical examination but not in the range of the eye movement tasks.

advertising. The demographics of the control and CII groups were comparable (table 1). Ethical approval was obtained from the Research Ethics Boards at the Hospital for Sick Children and the University Health Network, Toronto. The study was in accord with the Declaration of Helsinki guidelines.

Exclusion criteria were as follows: visual field defects on visual field confrontation testing, peripheral III, IV, or VI cranial nerve palsy, nystagmus on clinical examination in the range of the eye movement recordings, ear disease, psychiatric disorder, medication with drugs that might interfere with eye movements (e.g., sedatives), acute medical illness or acute illness from the effects of hydrocephalus in the CII group, amblyopia, ocular or neurologic disorders unrelated to CII, syringobulbia on MRI, or >10 shunt revisions.

Means and SDs for spina bifida and control groups on a visually guided upper limb pursuit task[24] were used to guide power calculations. Based on a two-sample t test power analysis, a sample size of 26 per group would detect significant difference in saccadic amplitude between the CII and control groups with 80% power $(1 - \beta)$ and 5% level of confidence (α).[25] The total sample number required was 52. Unequal numbers of participants in each group changed the power of the study to 82%.[25]

Spinal lesion level was determined from medical chart review and physical examination. Two groups were distinguished: upper spinal lesion level group (T12 and above, n = 6) and lower spinal lesion level group (L1 and below, n = 15).[26]

All participants had ventriculoperitoneal shunts. Three shunt groups were delineated. Group 1 had no shunt revisions, Group 2 had one shunt revision, and Group 3 had two or more shunt revisions.

Participants who had nystagmus on clinical examination within the range of the eye movement tasks were excluded, but seven participants were found to have low-amplitude gaze-evoked nystagmus (<2°) on eye movement recording that was clinically apparent only in eccentric gaze.

Nineteen participants with CII had artifact-free brain MRI scans. Different regions of interest in the brain were measured by one of us. Brain MRI measurements were calculated using computer software (Ataman software Inc., 1998) that measured distances or areas of the selected regions of interest on a T1- or T2-weighted midsagittal MRI.[27] The following measures were used as surrogate markers for cerebral and cerebellar dysmorphology in CII: 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 with typically developing children.[27]

Equipment and procedures. We recorded saccades with the El Mar eye tracker (El-Mar Inc., Downsview, Ontario, Canada), an infrared video eye tracking system that determines the horizontal and vertical eye position from the relative positions of multiple corneal reflections and center of pupil.[28-30] The optical components are mounted on a lightweight spectacle frame that weighed about 300 g. The video image is sampled at 120 Hz. The system accuracy is 0.5° with a linear visual range of ±40° horizontally and ±30° vertically. The system is free from drift and has a resolution (i.e., minimum detectable movement) of 0.1°. Horizontal and vertical head movements were recorded using a magnetic head tracker (Flock of Birds; Ascension Technology Corp., Burlington, VT).

Each participant was seated with his or her eyes in the central position, facing the center of a 45-cm computer monitor (SyncMaster 900 NF; Samsung) located 57 cm from the participant's cornea. The visual target displayed on the computer monitor was a 2-mm, white square light that subtended 12 minutes of arc. Stimulus luminance was 65 cd/m². The background monitor luminance was 0.01 cd/m². The laboratory was lit dimly. Participants' performance and alertness were monitored by TV and by an oscilloscope display of horizontal and vertical eye movements to provide feedback during the task. Eye movement positions were calibrated for each eye with the fellow eye occluded, at 14 fixation light points, separated by 3.3° visual angle and arrayed along the horizontal and vertical axes. Eyeglasses were removed prior to testing because they interfere with the function of the eye tracker. Uncorrected visual acuity in all cases was adequate for seeing and responding to the stimuli.

An eye patch was used to cover the nonpreferred (nonsighting) eye[31] in all participants. Movements of the viewing eye were measured. The target stepped between the center of the computer monitor and points located ±10° or ±15° horizontally and ±5° or ±10° vertically. Twenty target steps were presented at each amplitude and direction. The off-center locations and directions were presented randomly. Each trial started with the target on for at least 1 second before it stepped to the next location after a random interval between 0 and 0.5 second to avoid predictive saccades, which would confound measurement of saccade latency.[32,33]

Processing of eye movement data. The stimulus, head, and eye movements were digitized for off-line analysis. Stimulus, head, and eye velocity data were filtered using a 5-point Savitsky–Golay differentiator. Initial saccades were included in the analyses if they had a minimum velocity of 100°/s or were in the same direction as the target displacement, if the eye position trace shifted <0.5° from baseline during the 200 milliseconds prior to target displacement up to saccade onset, and if saccades occurred within a latency of 70 to 450 milliseconds to ensure that only visually directed nonanticipatory saccades were included. The beginning and end of saccades were marked automatically by computer software when eye velocity reached 30°/s. Each second of data was displayed on a computer monitor so that the automatic markings could be verified by inspection.

Mean horizontal or vertical head position was checked for each participant before, during, and after saccades to ensure that no head rotation of ≥0.5° induced the vestibulo-ocular reflex or changed the size of the required saccade. No saccade was associated with horizontal or vertical head rotation of ≥0.5°.

Analyses. For each participant, we calculated the means and SD of the initial saccadic amplitude gains, defined as the ratio of the first saccadic amplitude to target amplitude, and latencies. Saccade latencies were measured as the time between target step and the beginning of saccades, detected at the point when the eye velocity reached 30°/s. The saccadic peak velocity (PV)–amplitude (A) relationship, known as the main sequence,[34] was computed from scatter plots of individual saccades that were fitted to an exponential curve, $PV = V (1 - \exp [-A/C])$, for each participant, where V is the maximum velocity at the asymptote of the curve and C is a constant. This exponential equation served to best fit the nonlinear relationship relating saccadic amplitude to peak velocity.[35,36]

Analyses were done using a Statistical Package for Social Sciences (SPSS, Chicago, IL).[37] Between- and within-group data were compared using independent two-sample Student t tests for normally distributed data or Mann–Whitney U test for nonparametric data, Spearman correlation tests, and linear stepwise regression analyses. Bonferroni correction was applied when multiple comparisons were made.[25,38] Horizontal saccades to 15° target

Table 2 *Mean number of saccades and asymptotic peak velocities in control and Chiari type II malformation (CII) groups*

Parameter	Control group	CII group	p Value
Rightward saccades			
Mean no. of saccades	26 (7)	25 (7)	
Mean asymptotic peak velocity	521.2 (90.7)	485.1 (80.7)	0.13
Leftward saccades			
Mean no. of saccades	26 (6)	25 (9)	
Mean asymptotic peak velocity	537.4 (83.6)	539.4 (81.5)	0.90*
Upward saccades			
Mean no. of saccades	30 (7)	31 (5)	
Mean asymptotic peak velocity	466.9 (117.5)	420.9 (114.8)	0.17*
Downward saccades			
Mean no. of saccades	28 (6)	29 (6)	
Mean asymptotic peak velocity	435.7 (111.5)	458.5 (116.4)	0.52*

Values are given as °/s (1 SD).

* p Value on Mann–Whitney U test; the first p value was obtained on independent Student t tests. Significance was defined as $p < 0.01$.

Figure. Mean saccadic gains (A) and latencies (B) (ms; ±1 SE) for rightward (R), leftward (L), upward (U), or downward (D) target amplitudes in the control and Chiari type II malformation (CII) groups.

steps in the nasal field were analyzed, while temporally directed saccades to 15° target steps were excluded because of the blind spot. A statistical formula was used to take into account the variation in the number of saccades made by each subject for each target direction and amplitude (for more details see the supplementary material on the *Neurology* Web site at www.neurology.org).[39]

Results. There were no significant differences in saccadic amplitude gains, asymptotic peak velocities, or latencies between the CII and control groups (table 2; figure). Three participants in the CII group had abnormal saccadic gains, lying outside the 95% CIs of the mean saccadic gain of the control group. One participant had saccadic hypermetria (gain of about 1.6) to four of seven target amplitudes, and two participants had saccadic hypometria (gain of about 0.5) to two and five of seven target amplitudes. All three participants had clinically evident gaze-evoked nystagmus only beyond the range of eye movement recorded (±15°).

Three participants in the CII group had abnormally prolonged latencies lying outside the 95% CIs of the mean saccadic latency of control subjects. Two of them had gaze-evoked nystagmus, clinically evident only beyond the range of eye movements recorded. No significant group or individual differences in variability of saccades occurred between control and CII participants.

There were no significant differences in saccadic gains, asymptotic peak velocities, or latencies based on spinal lesion level or the presence of nystagmus. The number of shunt revisions did not affect saccadic gains, asymptotic peak velocities, or latencies. Linear stepwise regression analyses also did not show an effect for these variables on saccades. No significant correlations were found between saccadic gains, asymptotic peak velocities, or latencies and MRI parameters in participants with CII.
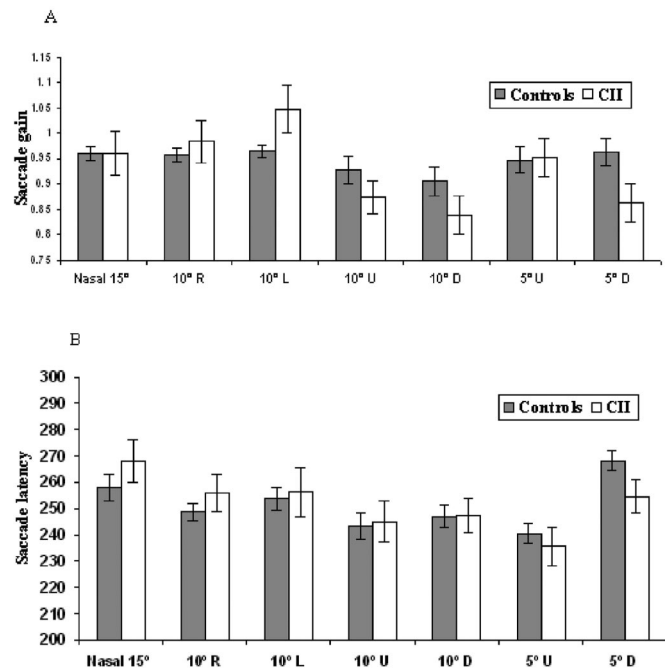
Discussion. No significant differences in saccadic gains, peak velocities, and latencies were found between the control and CII groups. Only 3 of 21 participants in the CII group had dysmetric saccades and saccades with prolonged latencies. The neural circuits involved in the processing of saccades are typically not adversely affected by the deformity of CII.

Saccadic dysmetria has been described in a few case reports or small case series of CI and CII.[18-23] The number of patients with saccadic eye movement abnormalities was 1 to 3 out of a total of 1 to 28 patients in those studies.[18-23] The number of subjects with CII studied was small, there were no controls, and eye movements were not recorded or were recorded by electro-oculography.

Several factors are known to be associated with worse outcome in spina bifida and CII. Upper spinal lesion is usually associated with worse cognitive, behavior, and limb movement disabilities and with more cerebellar and midbrain anomalies.[40-42] The number of shunt revisions was assumed to be a surrogate marker for the cumulative effects of severely raised intracranial pressure on the developing brain.[41] Gaze-evoked nystagmus was considered to indicate floccular and parafloccular involvement.[5] Statistical analyses showed that saccades were not adversely affected by any of these factors.

Neural circuits necessary for saccade processing are mostly normal in CII, perhaps because their function is not affected by the deformity of CII or because there is adequate neural reserve. The cerebellum may recalibrate eye movements to minimize

errors in the face of the chronic developmental and congenital deformity of CII.

Structure–function correlations between brain MRI and saccade metrics are sparse. Saccadic amplitude gain correlates with MRI volume of cerebellar vermis in healthy adult humans.[43] We found no correlation between saccadic parameters in CII and MRI measurements. Despite the anatomic abnormalities of the brainstem and cerebellum,[2,27] their physiologic function in saccadic processing is typically intact.

Recording eye movements in children is difficult and challenging. Restricting participants to those with verbal or performance IQ of >70 and excluding participants who had syringobulbia or nystagmus on clinical examination in the range of ocular motor recording served to select better-functioning individuals with CII.

The use of a noninvasive and well-tolerated eye tracker system in children, the relatively large number of participants, and the correlation of structural changes on MRI with function of the saccadic system provide a reliable quantitative assessment of the effects of CII deformity on the developing brain.

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