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Neuro-ophthalmology of type 1 Chiari malformation

Aasef G. Shaikh, MD,PhD¹ and Fatema F. Ghasia, MD²

¹Center for Neurological Restoration, Cleveland Clinic, Cleveland, OH

²Cole Eye Institute, Cleveland Clinic, Cleveland, OH

Abstract

Chiari malformation is a congenital deformity leading to herniation of cerebellar tonsils. Headache is a typical symptom of this condition, but patients with Chiari malformation often present with double vision and vertigo. Examination of eye movements in such patients often reveals nystagmus and strabismus. Eye movement deficits in the context of typical symptomatic presentation are critical clinical markers for the diagnosis of Chiari malformation. We will review eye movement deficits that seen in patients with type 1 Chiari malformation. We will then discuss the underlying pathophysiology and therapeutic options for such deficits.

Keywords

Eye movement; nystagmus; cerebellum; strabismus; brainstem

Background

Chiari malformation is characterized by herniation of posterior cerebellar vermis for more than 3 mm below the foramen magnum. Such malformation can be congenital or acquired through trauma. There are four subtypes of Chiari malformation, all of them feature herniation of posterior cerebellar vermis, but type 1 Chiari malformation has coexisting syringomyelia of cervical or cervicothoracic spinal cord. lumbar or lumbosacral myelomeningocele accompanies type 2 Chiari malformation is accompanied, occipital encephalocele is present in type 3 malformation, while the cerebellar hypoplasia is present in type 4 Chiari malformation [1]. Herniation of posterior cerebellar vermis is the hallmark of all four subtypes of Chiari malformation, hence, the corresponding ocular motor phenotype. The goal of this chapter is to discuss typical eye movement deficits in the patients with Chiari malformation. Although most evidence reported in this chapter came from the studies of type 1 Chiari malformation, the ocular motor abnormalities do not classify Chiari malformation in its various subtypes. Type 1 Chiari malformation typically presents in second or third decade of life; the headache is the most common symptom, but the visual symptoms are present in up to 80% of patients [2]. These visual symptoms include retro-orbital pain, blurred vision, photophobia, and diplopia. Type 1 Chiari malformation can be asymptomatic and discovered incidentally in 14-30% patients, up to 0.8 to 1%

patients undergoing MRI have coincidental (asymptomatic) cerebellar tonsil herniation [3]. Type 1 Chiari malformation presents with a variety of eye movement deficits [2,4,5]. These features along with the course of other symptoms can often clinically distinguish Type 1 Chiari malformation. The goal of this chapter is to review clinical features, pathophysiology, and treatment options for critical eye movement deficits in Type 1 Chiari malformation.

We will first review the role of the cerebellum in the control of eye movements. We will then apply these concepts to describe ocular motor abnormalities in Type 1 Chiari malformation.

Basic cerebellar organization and structure to function correlation

The input to the cerebellum projects to the Purkinje neurons in the cerebellar cortex via granule and molecular cell layer. The Purkinje neurons then project to the deep cerebellar nuclei, the primary output source of the cerebellum. Purkinje neurons in the dorsal aspect of the cerebellar vermis, also known as ocular motor vermis, are vital for the accuracy of rapid saccadic eye movements [6,7]. The ocular motor vermis projects to the medial most caudal fastigial nucleus. Lesions of these regions cause saccadic dysmetria where there is either undershooting or overshooting of eyes in relation to the target. Fastigial nucleus and adjacent posterior interpositus nucleus have an important role in binocular alignment [8-10]. Lesions of these nuclei cause strabismus. The flocculus and the paraflocculus of the vestibulo-cerebellum are vital for assuring image stabilization on the retina and ocular tracking [11]. The lesions of cerebellar flocculus result in drifts causing slow phase of nystagmus and impaired ability to pursuit smoothly moving target [11]. The nodulus and uvula of the posterior cerebellar vermis have an important role in increasing the frequency bandwidth of the head movements over which the vestibular-ocular reflex (VOR) is compensatory [12,13]. The network of brainstem and deep cerebellar neurons called the velocity-storage accomplishes this task. The velocity-storage is under direct inhibitory influence from the nodulus and ventral uvula. Lesions of these structures lead to prolonged rotational nystagmus and gravity-dependent spontaneous nystagmus [12-15]. Thus, each cerebellar structure has a unique role in control of various classes of eye movements.

In addition to the herniation of posterior cerebellar vermis, the Type 1 Chiari malformation also presents with structural malformation in the brainstem white-matter tracts. Therefore, it is not surprising that subjects with Type 1 Chiari malformation have a variety of ocular motor deficits. We will discuss these eye movement deficits in subsequent sections.

Nystagmus

Nystagmus is the most frequent eye movement deficit in Type 1 Chiari malformation. The patients with Chiari malformation present with various types of nystagmus; each type has unique pathophysiology and central correlate. The orientation of the eye-in-orbit determines the intensity of nystagmus. Typically there is an eye-in-orbit orientation, called null position where the nystagmus is minimal. Such null position is typically in straight-ahead orientation, but occasionally when eccentric it leads to compensatory head turning in the direction opposite of the null [2,16].

Gaze-evoked nystagmus

Clinical presentation—Gaze-evoked nystagmus is the most common type of nystagmus in patients with Type 1 Chiari malformation; it is present in up to 30% of the patients [2]. The gaze is stable when the eye-in-orbit position is straight-ahead, but the eccentric orbital position of the eyes triggers gaze-evoked nystagmus. The eyes drift from the eccentric position to the center, but the corrective beats bring the eyes back to the desired eccentric orbital position. Rebound nystagmus appears when the gaze is shifted back to straight-ahead orientation after sustained eccentric position. The gaze-evoked nystagmus or the rebound is neither sensitive nor specific for Chiari malformation. It merely suggests underlying deficits in the function of the cerebellum or the brainstem in the patient with Chiari malformation. Supplementary material 1 illustrates an example of gaze-evoked nystagmus with a rebound.

Pathophysiology—The gaze-evoked nystagmus is a disorder of ocular motor neural integrator [17]. We will first describe the neural integrator and then will discuss its significance in the pathophysiology of gaze-evoked nystagmus. When we make saccadic eye movements, the premotor structures in the brainstem fire a burst of neural discharge that typically encodes the eye velocity. This command is transmitted to the ocular motor neurons in the cranial nerve nuclei. The motor neurons then project to the extra-ocular muscles responsible for moving the eyes. Once the eyes reach eccentric orbital position, the tissue suspending the globe pulls the eyes back to the center due to inherent elastic properties. Therefore, the brain must generate additional signal after the velocity command to sustain the eyes in eccentric orientation. The neural integrators accomplish this function. The velocity signals also project to the network of neurons in the medial vestibular nucleus and the nucleus prepositus hypoglossi for the horizontal saccades and the interstitial nucleus of Cajal for the vertical and torsional saccades [18]. A neural network with unique synaptic organization present in these regions accomplishes the function of mathematical integration of the velocity pulse to the steady-state neural discharge [17,19]. The steady-state neural discharge, the output of the neural integrator, sustains the eyes at eccentric orientation. The optimal function of neural integrator not only depends on its internal connectivity, but also on peripheral feedback. The output of cerebellar flocculus significantly affects the neural integrator for horizontal eye movements. Cerebellar lesions therefore commonly present with the gaze-evoked nystagmus.

Figure 1 depicts an example of the gaze-evoked nystagmus. In this example, slow drifts in the position move the eyes away from the desired target location while rapid corrective movements (quick-phases) correct the drift (Figure 1A). The null position is straight-ahead (Figure 1A, B). The drift velocity increases as the eyes move away from the null and its direction reverses as the eye position shifts across the null (Figure 1B). The slow drifts in eye position are typically pathological while rapid corrections, the quick-phase, are physiological. The direction of the quick-phase characterizes the direction of the nystagmus.

Gaze-evoked nystagmus with shifted null position

The null position of the gaze-evoked nystagmus typically is straight-ahead. Occasionally, the null position is eccentric in the presence of asymmetric compression of the brainstem;

the shift of the null position is in the direction of more severe compression [16]. Figure 2 depicts an example of a brain MRI from a patient with Type 1 Chiari malformation with asymmetric brainstem compression. The compression was worse on the right side. She had gaze-evoked nystagmus, but the null position was on the right. As a result, she had baseline compensatory head rotation to the left. Figure 3 depicts an example of eye movements recorded from this patient. The black and gray traces represent horizontal eye positions while blue and cyan traces are vertical eye positions (Figure 3A). There are rightward drifts and leftward corrections during straight-ahead eye-in-orbit position. Nystagmus with much increased slow-phase velocity is present when the patient turned gaze to the left, but the gaze holding was stable during rightward eye in orbit position, suggesting a rightward shift in the null position. Figures 3B, C depict the summary of horizontal and vertical eye position dependence of the horizontal and vertical eye velocities, respectively.

Downbeat nystagmus

Clinical presentation—Downbeat nystagmus is present in 4-6% of patients with type 1 Chiari malformation [5,20]. As the name suggests, the pathological phase of this nystagmus drifts the eyes in the upward direction, downward quick-phase then follows the pathological drift. The downbeat nystagmus is present in primary gaze; it tends to get worse in down gaze, but upward gaze holding is stable. Supplementary material 2 depicts an example of downbeat nystagmus. Figure 4 illustrates eye position traces measured from the patient who had downbeat nystagmus. The typical presentation of the downbeat nystagmus is the propensity to fall forwards. Upward drifts of downbeat nystagmus tend to generate upward bias on the retinal representation of the external image. As a result, there will be forward compensatory shift in body posture and the propensity of forward falls.

Pathophysiology—We will now discuss the pathophysiology of downbeat nystagmus. The semicircular canal input project to the vestibular nucleus and then to the extra-ocular motor neurons. Each set of the semicircular canal is paired with a particular set of extra-ocular muscles and corresponding ocular motor neurons. The anterior semicircular canal is paired with the muscles driving upward eye movements. The pathway emerging from the anterior semicircular canal is under inhibitory control from the cerebellar flocculus. In patients with cerebellar lesions such as Chiari malformation affecting the cerebellar flocculus, there will be disinhibition of the anterior semicircular canal driven vestibulo-ocular reflex pathway. Such disinhibition leads to the tendency for the eyes to drift up followed by a correction in the form of downward quick-phase, hence the downbeat nystagmus [21].

Periodic alternating nystagmus

Clinical presentation—Periodic alternating nystagmus is a type of spontaneous horizontal nystagmus that is present in the central gaze but its direction reverses every 90-120 seconds.

Pathophysiology—Recall that nodulus and uvula has a role in extending the bandwidth of the vestibulo-ocular reflex by implementing GABA-mediated inhibition on the velocity-storage mechanism [13]. Therefore, the ablation of the cerebellar nodulus and uvula implies

excessive velocity storage and prolongs the decay of nystagmus induced by rotation [13]. Such animal models, if placed in darkness, develop periodic alternating nystagmus, but if allowed to view stationary environment the nystagmus is (visually) suppressed [13]. In humans with periodic alternating nystagmus, however, cerebellar lesions are not restricted to the nodulus and ventral uvula but also affect other parts of the vestibulocerebellum, such as the flocculus and paraflocculus [11,22,23]. All three areas of the vestibulocerebellum are affected in patients with type 1 Chiari malformation. The presence of periodic alternating nystagmus in subjects with type 1 Chiari malformation is not surprising.

Treatment of nystagmus

One or combinations of approaches are used for the treatment of nystagmus. These strategies include pharmacotherapy, use of optical devices, surgery, and treatment with somatosensory or auditory stimuli. Pharmacological treatment is the most successful means of treatment for most forms of nystagmus.

Gaze-evoked nystagmus

Gaze-evoked nystagmus is very common form of acquired nystagmus encountered in clinical practice. But the gaze-evoked nystagmus rarely causes visual symptoms because it is absent when the eyes are in the central (null) position. Therefore, the gaze-evoked nystagmus typically does not require specific treatment.

Downbeat nystagmus

It is speculated that the paucity of GABAergic inhibition of Purkinje neurons as a cause downbeat nystagmus. Hence, several forms of GABAergic pharmacotherapy was used for the treatment of downbeat nystagmus. Type-A GABA receptor agonist, clonazepam, improved downbeat nystagmus in two uncontrolled studies[24,25]. Type-B GABA receptor agonist, baclofen, was also tested for the treatment of downbeat nystagmus but with very limited success [26,27]. Likewise, gabapentin, an alpha-2-delta calcium channel antagonist suppressed downbeat nystagmus in one out of six patients [27]. Contemporary investigations evaluated 3,4-diaminopyridine in a randomized, controlled, cross-over trial involving 17 patients with downbeat nystagmus due to cerebellar degeneration, infarction, Chiari malformation, or unknown etiology [28]. The effects were assessed after the limited duration of treatment with 3,4-diaminopyridine. It was speculated that long-term treatment with aminopyridines might provide better success for the treatment of downbeat nystagmus [29-31]. Recent studies recommended treatment of downbeat nystagmus with 4-aminopyridine (5 mg to 10 mg three time a day) or 3,4-diaminopyridine (10 to 20 mg three times a day). We must emphasize that many studies of 4-aminopyridine revealed suboptimal results for the treatment of many forms of nystagmus, including downbeat nystagmus [28,29]. In our opinion, this could be due to insufficient length of therapy in these trials [31]. Cardiac arrhythmias are the most worrisome side effect of aminopyridines. Hence, every patient should have an electrocardiogram before and 30 minutes after the first ingestion of the drug in order to confirm that they do not develop prolongation of the corrected QT-interval.

Periodic alternating nystagmus

Baclofen is the treatment of choice for periodic alternating nystagmus. Baclofen at 5 to 10 mg three times a day dose completely abolishes the nystagmus in most patients [32,33]. Some patients with periodic alternating nystagmus might benefit from the addition of memantine [34].

Surgical decompression

Neuro-surgical decompression of symptomatic Chiari malformation improved the severity of downbeat nystagmus on many instances [5,35,36]. One study, however, suggested less favorable outcome of oscillopsia due to nystagmus after decompression surgery [37]. The latter study suggests a possibility of coexisting developmental alterations, in addition to brainstem compression due to herniation, leading to ocular motor deficits in Chiari malformation.

Strabismus

Clinical features and pathophysiology

Type 1 Chiari malformation can present with strabismus, typically esotropia[4,38,39]. A variety of pathophysiological changes can explain esotropia in patients with Type 1 Chiari malformation. For example, coexisting sixth nerve palsy can cause incomitant esotropia. Acquired comitant strabismus is also common. Divergence insufficiency can be the initial presentation in patients with minimal cerebellar tonsil herniation [40]. Divergent insufficiency can result in esotropia that worsens while distant viewing [40]. The skew deviation is also reported in patients with Chiari malformation [41]. Patients with Chiari malformation tend to have alternative hypertropia, abducting eye is higher as compared to adducting eye. Figure 5 depicts eye movements in a patient with Type 1 Chiari malformation and esotropia captured during monocular viewing condition. Leftward drifts were present during right eye viewing and vice versa.

Treatment

There are limited therapeutic options for strabismus in Chiari malformation. There is 30% success rate after the surgery [4]. The success rate increases if decompression precedes the strabismus surgery [36]. Typically it is recommended that strabismus surgery should be performed six to nine months after neurosurgical decompression of symptomatic Chiari malformation. Small comitant esotropia can be effectively treated with corrective prisms.

Afferent visual system

Type 1 Chiari malformation typically affects ocular motility, but the rare involvement of afferent visual system is also possible [42-44]. A structural abnormality in the posterior fossa in subjects with type 1 Chiari malformation can lead to malignant increases in cerebrospinal fluid pressure. Such deficit can present with acute onset of visual loss and malignant papilledema, requiring emergent cerebrospinal fluid shunt procedures for visual recovery [43,45,46]. Chronic type 1 Chiari malformation patients can present with thinning

of the retinal nerve fiber layer although evidence for such thinning is not robust using conventional quantitative techniques such as ocular coherence tomography [44].

Expert commentary

Type 1 Chiari malformation is a common congenital deformity leading to the variable clinical course. Eye movement deficits are recognized clinical entity but not commonly utilized clinical markers for establishing a diagnosis and measuring the impact of the treatment. Identification of typical and unusual eye movement deficits in Type 1 Chiari malformation supports the notion that it is not just the anatomical herniation and secondary compression, but there exist a possibility of abnormal connectivity in the brainstem. Quantitative assessments of eye movements in Chiari malformation are also utilized to delineate basic neurophysiology of the ocular motor system.

Five-year view

We anticipate more utilization of portable eye trackers to assess eye movement deficits objectively and to quantitatively determine the severity of functional impairment and therapeutic outcome. Future studies will objectively correlate eye movement deficits with high-resolution structural imaging of the cerebellum and its connections. Such structure to function correlation will enhance our understanding of the disease process and will allow better understanding of the physiology of eye movement control. The structure-to-function correlation will also define novel surgical approaches tailored to disease presentation in a given patient. In addition, we anticipate the establishment of comprehensive clinics for the care of patients with Chiari malformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key issues

- 1) Type 1 Chiari malformation is a common deformity of the nervous system.
- 2) Patients with Type 1 Chiari malformation commonly present with eye movement deficits, such as nystagmus and strabismus.
- 3) Gaze-evoked nystagmus is commonly seen, but it does not warrant treatment in most cases.
- 4) Downbeat nystagmus is also common. The effects on the quality of life may justify treatment with GABAergic pharmacotherapy.
- 5) Strabismus commonly leads to diplopia in patients with Chiari malformation.
- 6) Rare eye movement deficits in patients with Chiari malformation include shifted null of gaze-evoked nystagmus, seesaw nystagmus, and periodic alternating nystagmus.

Figure 1.

Example of gaze-evoked nystagmus. Panel A depicts an example of gaze-evoked nystagmus during one second epoch. Panel B depicts eye-in-orbit position dependence of drift velocity. Panel B also illustrates reversal of drift directions on two sides of the null. This figure was adopted (with permission) from Ghasia, et al., 2014 [16].

Figure 2. Brain MRI in fluid-attenuated inverse recovery sequence suggesting type 1 Chiari malformation. The malformation is shown in sagittal (A) and axial (B) sections. This figure was adopted (with permission) from Ghasia, et al., 2014 [16].

Figure 3.

Shifted null position of the gaze-evoked nystagmus. (A) Eye positions are plotted on the y-axis while time is plotted on the x-axis. Horizontal eye positions at all gaze orientations (except 15 degrees to the right) have drifts towards the right and quick-phase to the left. This example suggests gaze-evoked nystagmus with null position shifted approximately 15 degrees to the right. (B) Vertical and horizontal eye-in-orbit position dependence of horizontal drift velocity of the gaze-evoked nystagmus. Horizontal eye-in-orbit position is plotted on the x-axis while vertical eye position is on the y-axis. The shades of orange depict drift velocity. (C) This panel summarizes vertical and horizontal eye-in-orbit position dependence of the vertical drift velocity. This figure was adopted (with permission) from Ghasia, et al., 2014 [16].

Figure 4. Example of downbeat nystagmus. Black lines depict vertical eye movements and gray lines are horizontal eye movements. Nystagmus is maximal in downward eye-in-orbit position, but it is minimal in an upward position.

Figure 5.

Monocular viewing condition leads to drift in the position of the covered eye (arrows) under monocular viewing condition. These drifts are irregular and they are superimposed upon the drifts in the eye positions that comprise nystagmus. This figure was adopted (with permission) from Ghasia, et al., 2014 [16].