Impaired Vertical Phoria Adaptation in Patients with Cerebellar Dysfunction

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PURPOSE. To determine whether phoria adaptation to a vertical prism disparity is altered in patients with cerebellar dysfunction.

METHODS. With a computer-aided haploscope, adaptive responses of fusion-free eye position to a 10- or 30-minute period was measured in subjects wearing a 3-prism diopter vertical prism over one eye. Thirteen patients with well-documented cerebellar diseases who did not have manifest ocular misalignment or limited versional eye movement and age-matched healthy subjects participated.

RESULTS. The mean ± SD percentage of vertical phoria adaptation was 13% ± 2.2% and 20% ± 16% for the 10- and 30-minute adaptations, respectively. These levels were significantly smaller than the respective ones in the age-matched control group (P < 0.001, repeated measures MANOVA). Seven (54%) of 13 patients, including two with genetically confirmed pure cerebellar lesions (spinocerebellar ataxia type 6), showed markedly reduced responses to both the 10- and 30-minute adaptations. In all three patients with acute cerebellar ataxia, the adaptive response was improved at the same time as remission of cerebellum-associated neurologic deficits.

CONCLUSIONS. Phoria adaptation to vertical binocular disparity is frequently impaired in patients with cerebellar dysfunction. These results bolster the hypothesis that phoria adaptation is a cerebellum-dependent response. (Invest Ophthalmol Vis Sci. 2002;43:673–678)

Phoria is a physiological resting position of vergence, appearing when all vergence-related information (i.e., binocular disparity, retinal image in blur, and proximal cues) are eliminated. The impressive aspect of phoria is its adaptive function, or phoria adaptation.1,2 It is thought that phoria adaptation maintains ocular alignment, compensating for developmental, environmental, or pathologic alternations in the binocular mechanism (e.g., an increase in the interpupillary distance with age, the anisometric effect of spectacles, extracocular muscle diseases, or their associated dominant nerve palsy).

Nevertheless, the anatomic substrate underlying phoria adaptation is little understood. Milder and Reinecke,3 who first examined phoria adaptation in patients with cerebellar diseases, concluded that the cerebellum plays a central role in phoria adaptation. Many types of oculomotor adaptation appearing in the saccade,4 smooth pursuit,5 and vestibulo-ocular reflex6,7 require an intact cerebellum for normal performance. Patients with cerebellar lesions are expected to show an abnormal phoria adaptation response. However, Hain and Leubke8 studied a larger patient group and concluded that some lesions other than those in the cerebellum are involved in dysfunctional phoria adaptation.

We believe such conflicting results are partly due to the unstable nature of horizontal phoria. Through the accommodative vergence (ratio of accommodative convergence to accommodation [AC/A]) cross-link, the phoria position is continuously altered horizontally by accommodative fluctuation (<0.5 D in amplitude9), which corresponds to a phoria change of 1.8 prism diopters [PD] when calculated with the mean AC/A ratio of 3.5 PD/D). This extent of phoria change could be a problem, when compared with the rather small prism disparities previous researchers3,8 used to induce phoria adaptation: 6 and 8 PD, respectively. To overcome this problem, researchers in earlier studies used a special technique—the brief-flash Maddox rod procedure—instead of the commonly used Maddox rod or Lancaster red-green test.10

Another important factor that could affect the results in such a comparative study is age-bias. Winn et al.11 demonstrated that the horizontal phoria adaptation response significantly declines as a function of increasing age. In fact, Hain and Leubke8 mentioned a trend in patients who showed poor adaptation to be older than those who showed normal adaptation, but, unfortunately, they did not adjust for age bias in their statistics.

Phoria adaptation also occurs in response to a vertical prism disparity. Recent empiric evidence has shown that vertical phoria adaptation works to maintain binocular alignment across the field of gaze in a much more sophisticated manner than previously thought: Vertical phoria adaptation can be specific to head position, conjugate eye position, and horizontal vergence posture.12–17

The dynamic properties of vertical phoria adaptation, as well as vertical vergence movement itself,18 resemble those of the horizontal mechanism.19 However, the amount of the prism disparity that could be provided as a stimulus is limited because of the rather small range of vertical fusion. In contrast, the vertical phoria position, unlike the horizontal one, is barely influenced by accommodative fluctuation, which may contribute to better precision in phoria measurement. We thus think that investigation of vertical phoria adaptation in patients with cerebellar dysfunction will provide information to clarify whether the cerebellum contributes to phoria adaptation.

Similar to the results shown for horizontal phoria adaptation,11 our previous study in healthy subjects20 showed that the vertical phoria adaptation response decreases with age, approximately 1% per year. In the current study, we examined vertical phoria adaptation in 13 patients with well-documented cerebellar diseases and in age-matched control subjects, using a computer-aided haploscope. The mean magnitudes of the adaptation were compared, the relationship among individual responses to the neurologic findings was analyzed in the patient group, and the role of the cerebellum in phoria adaptation was considered.
Subjects and Methods

Subjects

Thirteen consecutive patients with cerebellar diseases (eight men and five women, mean age ± SD: 48.2 ± 16.0 years; range, 21–65) and 15 age-matched, healthy volunteers (mean age, 47.5 ± 15.8 years) participated. The patients’ diagnoses included spinocerebellar ataxia type 6 (SCA6), dentatorubral pallidoluysian atrophy (DRPLA), olivopontocerebellar atrophy (OPCA), and acute cerebellar ataxia (ACA).

We excluded subjects from this study according to the following criteria: (1) corrected visual acuity less than 20/30, (2) manifest deviations of the eyes, (3) unable to fuse through a 3-PD vertical prism, (4) stereoaucy poorer than 240 seconds, (5) any detectable vertical heterophoria, and (6) dementia. Informed consent was obtained from each of the patients and volunteers after explanation of the purpose and methods of this study, according to the tenets of the Declaration of Helsinki.

Ophthalmic, Neurologic, and Genetic Examinations

A full ophthalmic evaluation was performed on all subjects. Evaluation included best-corrected visual acuity, cover tests, and stereo acuity testing with the TNO random-dot test. The vertical fusional range (break point) was determined with a bar-prism, Bagolini striated glasses, and a near-point source of light. A full neurologic examination, including magnetic resonance imaging (MRI), was performed on all patients. Diagnoses of SCA6 and DRPLA were confirmed by detecting expansion of a CAG repeat on chromosome 19p and 12p, respectively.

Adaptation Procedures

A 3-PD (1.65°) Fresnel membrane prism (3M Health Care, St. Paul, MN) was used to introduce a vertical fusional disparity. We affixed it, base down, to a spectacle lens over the right eye. If the subject did not have spectacles, some with plano lenses were provided. Subjects were instructed to wear the prism and engage in normal visual tasks, such as viewing television during adaptation periods of 10, and an additional 20 minutes, which corresponded to 10- and 30-minute adaptations, respectively. Preservation of binocular single vision during the adaptation periods was carefully checked every 5 minutes with Bagolini striated glasses and a near-point source of light.

Phoria Measurement

We measured phorias at the following times, relative to prism wearing: (1) immediately before, (2) immediately after, (3) after 10 minutes, and (4) after 30 minutes, using a computer-aided haploscope (Fig. 1). During the phoria-measurement period of 3 minutes, fusion was completely interrupted with a diagonal reflecting prism placed in front of the right eye. A red circular target (diameter: 0.5°) with 12-point characters surrounding it was seen with only the left eye. A green cross target (end-to-end width: 2.0°) projected on a dimly lit video display (model PC-KD854n; NEC, Inc., Tokyo, Japan) was seen by only the right eye. The display frame was masked with a black baffle. The viewing distance to the targets was 47 cm, and resolution of the target presentation on the display was 0.04°/pixel. Subjects’ heads were stabilized with a headband and a chin rest to minimize alternation of head position between the measurement sessions. Subjects were instructed to keep alignment of the two targets as precisely as possible by moving the target on the display with a trackball. The coordinates of the target on the display were stored every 10 seconds. The target-presenting and data-acquisition programs specially written (N88BASIC; NEC, Inc., Tokyo, Japan) on a microcomputer (model PC286; Epson, Tokyo, Japan).

The subjects usually needed 10 to 30 seconds to establish fine alignment of the targets by manipulating the track ball. Reportedly, the phasic component of fusional vergence persists approximately 15 to 45 seconds after fusional disparity is eliminated by occluding one eye.25,26 Coincidentally, our vertical measurements appeared to stabilize in this period (Fig. 2). Therefore, we took vertical measurements from 50 to 140 seconds (n = 10) and regarded their average as a representative amount of vertical phoria. The variation in the vertical measurements during this period was approximately 0.23 PD (SD) in most cases, which was eight times smaller than the horizontal amounts.

We obtained the amount of vertical phoria adaptation (in degrees) by subtracting the baseline vertical measurement (2) from one that was taken after the adaptation (3 or 4). The size effect due to the spectacles was individually calibrated based on alternations in the vertical measurements before (1) and immediately after (2) wearing the prism.

Results

Averaged time courses of vertical phoria adaptation in the patient and control groups are shown in Figure 2. In the patient group, the mean ± SD percentage of vertical phoria adaptation in response to the 3-PD vertical prism was 13% ± 22% and 20% ± 16% for the 10- and 30-minute adaptations, respectively. The respective percentages for the control group were 46% ± 11% and 57% ± 16%. The patient group had a significantly smaller mean magnitude of response than the control group (P < 0.0001, repeated measures multivariate analysis of variance [MANOVA]). Between the 10- and 30-minute adaptations, there was no significant difference in the magnitude in the patient group, whereas the magnitude significantly increased with time in the control group (P = 0.029, paired t-test).

Table 1 shows individual amounts of vertical phoria adaptation. The 95% limits of normal range evaluated in our control subjects were 25% to 67% and 26% to 89% for the 10- and 30-minute adaptations, respectively. These amounts indicate considerable intersubject difference in vertical phoria adaptation ability, which is consistent with earlier reports.19,24 Compared with this normal range, 7 (54%) of 13 patients (patients 1, 2, 3, 5, 6, 10, and 13) showed significantly smaller responses for both the 10- and 30-minute adaptations, whereas two patients (15%; patients 8 and 9), in whom MRI showed mild atrophy of the cerebellum and pons, had normal responses.
The three patients with acute cerebellar ataxia (patients 11, 12, and 13) showed abnormally poor response of vertical phoria adaptation, either to 10 or 30 minutes’ adaptation at the initial visit. However, all three patients showed increased magnitude of vertical phoria adaptation to both the 10- and 30-minute adaptations after remission of the gait ataxia and other cerebellum-associated neurologic deficits, which took 1 to 5 months (Table 1).

**DISCUSSION**

This study demonstrated that phoria adaptation to vertical prism disparity is frequently impaired in patients with cerebellar dysfunction, even when they do not have manifest ocular misalignment, limited versional eye movement, or degradation of vertical fusional amplitude. The mean amplitude of vertical phoria adaptation in the patient group was significantly smaller than that in the control group. Compared with the 95% limits of the normal range that were determined with age-matched control subjects, 7 (54%) of 13 patients showed abnormally poor responses for both the 10- and 30-minute adaptations.

In measuring vertical phoria adaptation, some difficulty arose from its rather small magnitude. The normal vertical fusional response typically breaks at 3 to 4 PD and recovers at 2 PD, and, accordingly, the prism disparity that can be provided to elicit phoria adaptation is limited.12-17,19,24 However, our measurement method of vertical phoria adaptation has advantages. First, vertical phoria during a single measurement period was markedly stable. Because we averaged 10 consecutive measurements, the precision of a single phoria determination was theoretically deduced to be approximately 0.1 PD (SD). Second, our computer-aided haptoscope with a trackball system provided little help regarding the target locus on the display; the responses were effectively masked to the subjects. Third, vernier acuity may contribute to improved precision of the measurement while the subject determines whether the two targets are aligned. We thus think that the precision of our measurements was adequate for the purpose of this study.

The reported time required for full adaptation to vertical prisms differs among researchers. Henson and North10 showed that adaptation to a 2-PD vertical prism was completed in 3 minutes, whereas Eskridge24 reported that it required 30 to 120 minutes. Schor et al.12 proposed two independent systems for vertical phoria adaptation: a spatially global and a local system. The former system shifts the vertical phoria uniformly across the field of gaze and takes several tens of minutes to complete. The latter system tunes the phoria selectively to the position, depending on the demands of the disparity stimulus, and takes more than several hours to complete. Because we used a uniform prism as a stimulus, the response we observed was mainly global. Coincidentally, our previous study found no significant difference in the amount of vertical phoria adaptation between the 30- and 60-minute adaptations, whereas there was a significant difference between the 10- and 30-minute adaptations (increased with time).20 In this study, for ease of clinical application, we set the duration of the adaptation periods to 10 and 30 minutes, which seemed to be the minimum requirement for adaptation saturation.

Besides the smaller mean amount of adaptation, we found that the responses of the patient group showed some individual idiosyncrasies that led to the wider variation in their response (Fig. 2). A negative response, during which the phoria shifted to the opposite direction of the given prism disparity, was observed in three patients (patients 1, 2, and 12) for the 10-minute adaptation only. Magnitudes of response for the 30-minute adaptation were smaller than those for the 10-minute adaptation in three patients (patients 3, 11, 13). Such
negative responses or a decreasing amount of response over time, even though the rather long period (3 minutes) in our testing procedure interrupted the adaptation process of the subjects, are rarely seen in healthy subjects. Normally, the rate of phoria adaptation decays exponentially with time, which is one indication of the presence of a neural integrator with a long time constant. It is interesting to note that such odd responses were also reported elsewhere in horizontal phoria adaptation in patients with cerebellar dysfunction. It is possible that lesions in the cerebellum make the integrators for phoria adaptation unstable or fatigue easily, as well as lowering their gain.

The question of exact anatomic localization is always a difficult one with clinical lesions, although we have computed tomographic (CT) and MRI evidence. This is because most patients have multiple or diffuse lesion(s). Our MRIs showed involvement of the brain stem and pons in many patients with spinocerebellar degeneration. In our patients, however, the intact Heron’s law of conjugacy and no limitation of versional eye movements suggests preservation of the ocular motor mechanism in the brain stem. The other eye movement disorders observed in our patients (i.e., saccadic dysmetria, impairment of smooth pursuit, and pathologic nystagmus), are reportedly all attributable to lesions in different parts of the cerebellum.

A genetic test found that patients 1 and 2 had a CAG repeat expansion on chromosome 19p, which refers to SCA6. SCA6 is autosomal dominant and leads to slowly progressive cerebellar ataxia without multisystem involvement. Pathologically, severe loss of Purkinje cells was reported, particularly in the

For Table 1 and Table 2, please refer to the original text for the full table details.
vermis, and disoriented axonal arrangement and many torpedoes, axonal swelling of Purkinje cells, were found in the granular layer and white matter. Coincidentally, our MRI images of these patients showed pure cerebellar atrophy without pontine lesions, which was consistent with the genetic test results indicating a CAG repeat expansion on chromosome 19p (SCA6). These patients showed markedly reduced responses during both the 10- and 30-minute adaptations (Table 1).

Acute cerebellar ataxia is an inflammatory syndrome of cerebellar dysfunction that may reflect infectious, postinfectious, or postvaccination disorders, and it is self-limiting in most cases. Our three patients with this disease, after remission of gait ataxia and other cerebellum-associated neurologic deficits, showed greater responses of vertical phoria adaptation than those observed at the initial visit. Such response recovery paralleling well-documented cerebellar symptoms suggests that vertical phoria adaptation is a cerebellar function.

Information from animal studies regarding phoria adaptation is limited. Judge demonstrated that monkeys with floccular and ventral paraflocculus lesions can still achieve horizontal phoria adaptation. Nevertheless, deep cerebellar nuclei are left as possible critical cerebellar structures influencing phoria adaptation. Recent electrophysiological studies have reported that a variety of supranuclear regions of the brainstem, and possibly the pons and cerebellum, may serve as inputs to the adaptive system for vergence control.

In understanding the mechanisms underlying ocular misalignment associated with cerebellar dysfunction, or in planning its treatment, the limited function of vertical phoria adaptation should probably be taken into account. For example, skew deviation, usually a comitant vertical misalignment of the eyes, is frequently associated with cerebellar dysfunction, although a variety of ocular motor disorders have been reported. A comitant or noncomitant vertical deviation, termed alternating skew deviation on lateral gaze (left hyper for the right gaze and right hyper for the left gaze), has also been reported in patients with lesions in the cerebellar pathways to the cervicomedullary junction. Theoretically, unilateral or bilateral lesion(s) of otolith inputs could explain the skew and alternating skew deviations, respectively. In an experiment with monkeys, in contrast, cerebellectomy without involving the primary otolith pathways caused persistent alternating skew deviation. We do not have any direct evidence from patients with skew deviation, because we excluded pa-
tients with manifest ocular misalignment from this study. Prismatic compensation for ocular misalignment could induce another spatially global or local vergence adaptation. However, it is conceivable that impairment of vertical phoria adaptation due to cerebellar lesions may allow an underlying imbalance of the otolith inputs to manifest itself.

In conclusion, this study revealed that phoria adaptation to a vertical binocular disparity is frequently impaired in patients with cerebellar dysfunction. We have no evidence about whether cerebellar lesions respond equally to horizontal and vertical fusional disparities, and therefore the previously mentioned controversy regarding horizontal phoria adaptation remains unresolved. Our results, however, bolster support for the hypothesis that phoria adaptation is a cerebellum-dependent response.3

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References