Primary Position and Listing's Law in Acquired and Congenital Trochlear Nerve Palsy

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Purpose. In ocular kinematics, the primary position (PP) of the eye is defined by the position from which movements do not induce ocular rotations around the line of sight (Helmholtz). PP is mathematically linked to the orientation of Listing's plane. This study was conducted to determine whether PP is affected differently in patients with clinically diagnosed congenital (conTNP) and acquired (acqTNP) trochlear nerve palsy.

Methods. Patients with unilateral conTNP ($n = 25$) and acqTNP ($n = 9$) performed a modified Hess screen test. Three-dimensional eye positions were recorded with dual search coils.

Results. PP in eyes with acqTNP was significantly more temporal (mean: 21.2°) than in eyes with conTNP (6.8°) or healthy eyes (7.2°). In the pooled data of all patients, the horizontal location of PP significantly correlated with vertical noncomitance with the paretic eye in adduction ($R = 0.59$). Using a computer model, PP in acqTNP could be reproduced by a neural lesion of the superior oblique (SO) muscle. An additional simulated overaction of the inferior oblique (IO) muscle moved PP back to normal, as in conTNP. Lengthening the SO and shortening the IO muscles could also simulate PP in conTNP.

Conclusions. The temporal displacement of PP in acqTNP is a direct consequence of the reduced force of the SO muscle. The reversal of this temporal displacement of PP, which occurs in some patients with conTNP, can be explained by a secondary overaction of the IO muscle. Alternatively, length changes in the SO and IO muscles, or other anatomic anomalies within the orbit, without a neural lesion, may also explain the difference in location of PP between conTNP and acqTNP. (*Invest Ophthalmol Vis Sci.* 2003;44:4282–4292) DOI:10.1167/iovs.02-1181

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Damage to the trochlear nerve leads to paresis of the superior oblique muscle and consequently to a hyperdeviation with the affected eye higher. The vertical deviation between the two eyes is at its maximum when the paretic eye is adducted and depressed. Furthermore, because the action of the superior oblique muscle contains a major intorsional component,[1] the affected eye shows an abnormal change of torsional orientation as a function of the elevation of the line of sight, with maximum extorsion in downgaze. This particular pattern of noncomitant cyclovertical misalignment is typical in acquired trochlear nerve palsy, particularly of recent onset. If, however, the hyperdeviation of the affected eye during vertical gaze in adduction is comitant, or even increases with elevation of the line of sight, this configuration of vertical strabismus is more typical of congenital trochlear nerve palsy, usually noted early in life. It is uncertain, however, whether the pattern of congenital trochlear nerve palsy can truly be ascribed to a deficit of trochlear nerve function.[2,3] Over time, in patients with acquired trochlear nerve palsy, a pattern of misalignment can develop similar to that of congenital trochlear nerve palsy.

In individual patients, it is difficult to distinguish between acquired and congenital trochlear nerve palsy, because many of the commonly applied criteria are based on clinical impressions and have not been validated surgically or by magnetic resonance (MR) imaging.[4] For instance, the sudden occurrence of double vision does not rule out congenital trochlear nerve palsy, because, in these patients, fusional mechanisms can suddenly decompensate at a later stage in life.[5] An increasing vertical deviation between the two eyes with downgaze with the paretic eye in adduction suggests acquired,[6,7] a recent head trauma suggests acquired,[8] a large vertical fusional amplitude suggests congenital,[9] and facial asymmetry with the shorter side of the face on the side of the customary head tilt suggests congenital trochlear nerve palsy,[10] but none of these criteria for the differential diagnosis is absolute.[4,11,12]

In this study, we asked how Listing's law of ocular motility is affected in trochlear nerve palsy. Listing's law describes the mathematical relation between the horizontal and vertical direction of the line of sight and ocular torsion.[13] Specifically, all axes of single rotations from the reference eye position (usually the straight-ahead position) to any other position of ocular fixation approximately lie in a plane, the so-called Listing's plane.[14,15] From the three-dimensional (3D) orientation of Listing's plane, the primary position of the eye, as strictly defined in the field of ocular kinematics, can be determined.[16] Primary position represents the unique reference position from which horizontal and vertical ocular positions can be reached without a rotation of the eye around its line of sight.[13,17] If Listing's plane does not lie parallel to the frontal plane of the head, primary eye position is displaced from the straight-ahead position in the direction of the tilt of Listing's plane. In other words, the gradient of ocular torsion along vertical and horizontal gaze directions reflects the location of primary position. If, for instance, an eye intorts when moving upward, its axis for the overall vertical–torsional rotation is tilted outward. Thus, primary position is located temporally from the vertical meridian. Or, if there is increasing intorsion of the eye with abduc-

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tion, the axis of the horizontal–torsional rotation is tilted forward, and therefore the primary position is located below the horizontal meridian. Only if the primary positions of the two eyes coincide, will the eye movements in Listing's plane fail to induce cyclodisparity during fixation of eccentric targets at infinity. For geometrical reasons, the primary positions of the two eyes must diverge to minimize cyclodisparity during near fixation—that is, the Listing's plane tilts outward.[18]

Generally, Listing's law can be affected by trochlear nerve palsy in two ways: (1) 3D ocular positions may deviate from Listing's plane in such a way that Listing's law is violated; and (2) Listing's law is still valid, but the orientation of Listing's plane may change, which implies an abnormal location of primary position. Because the action of the superior oblique muscle includes a torsional component, we hypothesized that trochlear nerve palsy must have an effect on Listing's law. Furthermore, we expected that the effect would be different in patients with acquired than in patients with congenital trochlear nerve palsy. Specifically, we assumed that in patients with acquired trochlear nerve palsy, any change of Listing's plane could be predicted mainly by the weakened superior oblique muscle. In patients with congenital trochlear nerve palsy, on the contrary, abnormal or compensatory function of more than one extraocular muscle or abnormal mechanical factors in the orbit may contribute to the change in Listing's plane. Using a current computer model of the eye plant (MatLab implementation[19] of the Orbit model[20]; The MathWorks, Natick, MA), we replicated the 3D kinematics of eye positions observed in patients with acquired and congenital trochlear nerve palsy. Based on our clinical experience, we introduced realistic primary and compensatory changes of force and length in individual eye muscles and qualitatively compared the output of the model with the patients' data.

Part of this work has been published previously in abstract form.[21]

METHODS

Subjects

Thirty-four patients (age range, 15–80 years, 10 female) with trochlear nerve palsy were studied. The clinical diagnosis of trochlear nerve palsy was based on the three-step procedure described by Parks,[22] including Bielschowsky head tilt testing.[23] Twenty patients were tested at the Johns Hopkins Hospital (Baltimore, MD), and 14 at Zurich University Hospital (Zurich, Switzerland). In all patients, intermittent or constant vertical double vision was present for more than 6 months. The comparison group consisted of 15 healthy subjects (N1–N15; age range, 23–56 years, 5 female), of which 10 were tested in Baltimore and the other 5 in Zurich. Informed consent from patients and healthy subjects was obtained after the experimental procedure was explained. The experimental protocols were approved by the Johns Hopkins Joint Committee on Clinical Investigation or by a local Ethics Committee at Zurich University Hospital and adhered to the Declaration of Helsinki for research involving human subjects.

Before analyses, three of the authors, experienced strabismus surgeons and neuro-ophthalmologists (HS, KL, AVM), partitioned the 34 patients into two groups with acquired ($n = 9$) or congenital ($n = 25$) trochlear nerve palsy, based on the relative criteria listed in Table 1. Two authors (HS, AVM) reviewed the charts of the Baltimore patients and another of the authors (KL), the charts of the Zurich patients. In a second stage, two authors (HS, KL) reviewed all charts to ensure the consistency of the clinical diagnosis between the Baltimore and Zurich patients. The patients were assigned to the "acquired" or "congenital" group if all criteria ("sure") or most of the criteria ("likely") pointed toward one diagnosis. (The designations acquired and congenital are arbitrary [as defined by our criteria] and are used with the caveats outlined in the introduction and the Methods section.) For example, a diagnosis was considered "likely to be congenital," if a minor head trauma had occurred, but facial asymmetry and vertical fusional amplitude pointed toward "congenital." Acquired trochlear nerve palsies were the result of head trauma ($n = 6$), cerebral vasculopathy ($n = 2$), or a tumor along the fourth cranial nerve ($n = 1$).

TABLE 1. Relative Criteria Used to Partition Patients with Unilateral Trochlear Nerve Palsy into Acquired and Congenital Disease Groups

Criteria	Acquired	Congenital
History of trauma or lesion to the trochlear nerve	+	−
Large vertical fusional amplitude (>5 prism diopters)	−	+
Facial asymmetry	−	+
Head tilt on old photographs (if available)	−	+

Experimental Setup

The experimental setups in Baltimore and Zurich were identical, unless stated otherwise. Ocular rotations of both eyes around all three principal axes (torsional, roll, *x*-axis; horizontal, pitch, *y*-axis; vertical, yaw, *z*-axis) were simultaneously recorded with dual search coils manufactured by Skalar (Delft, The Netherlands). The field system consisted of a cubic coil frame of welded aluminum that produces three orthogonal magnetic fields with frequencies of 55.5, 83.3, and 41.6 kHz and intensities of 0.088 Gauss. Amplitude-modulated signals were extracted by synchronous detection (Remmel-type system built by Adrian G. Lasker, Johns Hopkins Hospital, Baltimore, MD). The bandwidth of the system was 0 to 90 Hz. The side length of the coil frame was 1.02 m in Baltimore and 1.40 m in Zurich. Peak-to-peak noise signals in all three principal directions after calibration, as measured by a dual search coil placed in the center of the magnetic frame, were ±0.05° in Baltimore and ±0.1° in Zurich.

Calibration Procedure

Dual search coils were calibrated in vitro on a gimbal system before each experiment. Details of the procedure are published elsewhere.[24] The 3D eye position in the magnetic coil frame was expressed in rotation vectors.[16] A rotation vector, $\mathbf{r} = (\mathbf{x}, \mathbf{y}, \mathbf{z})$, describes the instantaneous orientation of the eye as a single rotation from the reference position. The vector is oriented parallel to the axis of this rotation, and its length is defined by $\tan(\rho/2)$, where ρ is the angle of rotation. The signs of rotation vectors are determined by the right-hand rule—that is, clockwise, leftward, and downward rotations, as seen from the subject, are positive.

Experimental Procedure

Subjects were seated inside the magnetic coil frame so that the center of the interpupillary line coincided with the center of the frame. The head was immobilized with an earth-horizontal bite bar. Dual search coils were mounted on both eyes after the conjunctiva and cornea were anesthetized with proparacaine HCl 0.5% (Ophthetic; Allergan, Irvine, CA). During measurements, subjects monocularly fixed on light dots on a tangent screen at a distance of 1.24 m at its center, while first the right and then the left eye was covered. The dots were located straight ahead and at eight eccentric positions (vertical and horizontal coordinates, in degrees: [0,20]; [20,20]; [20,0]; [20, −20]; [0, −20]; [−20, −20]; [−20, 0]; [−20, 20]). Voltages related to the orientation of the eye coils in the magnetic coil frame were digitized with a 12-bit analog-to-digital converter at 500 to 1000 Hz and written to a hard disc. The data were analyzed off-line on computer (MatLab, ver. 6.0; The MathWorks).

Data Analysis

The nine data clouds of rotation vectors associated with target fixations were selected with an interactive computer program. The median 3D

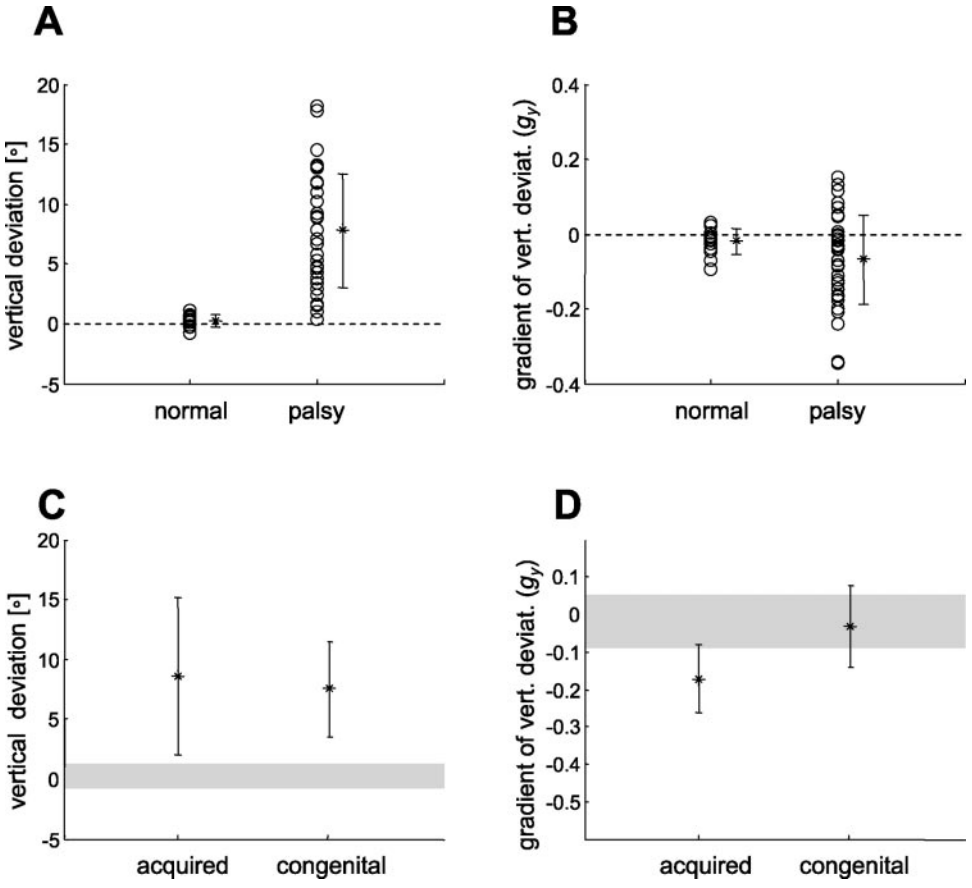

FIGURE 1. Summary plot of vertical deviation with the left eye viewing and the right eye covered. In the patients, if the left eye was paretic the data were mirrored, so that the paresis was always referred to the right eye. Normal, healthy subjects; palsy, patients with acquired or congenital trochlear nerve palsy; acquired, patients with acquired trochlear nerve palsy; congenital, patients with congenital trochlear nerve palsy. *Open circles*: data for individual subjects. *Asterisks* with error bars: averages ±1 SD. (**A**) Vertical deviation during straight-ahead fixation of the left eye. Positive values correspond to right eye-over-left eye position. (**B**) Gradient of vertical deviation g_y, when the right eye is covered and the viewing left eye is turned 20° to the left and fixes on the targets along the vertical line. A negative gradient, g_y, corresponds to an increasing right eye-over-left eye position with downgaze. (**C**) Average vertical deviation ±1 SD during straight-ahead fixation of the left eye. *Shaded area*: average ±2 SD from the comparison group of healthy subjects. (**D**) Average gradient of vertical deviation g_y ±1 SD, when the right eye is covered and the viewing left eye is turned 20° to the left and fixes on the targets along the vertical line. *Shaded area* as in (**C**).

rotation vector was then computed for each target point. In the patients, the data were mirrored between the two eyes if the left eye was paretic. Thus, for further analysis, the right eye was always the paretic and the left eye always the unaffected eye.

To compare parameters statistically among the three groups of subjects, we used one-way analysis of variance (MatLab function: anova1.m). If the outcome of ANOVA testing was statistically significant ($P < 0.05$), but visual inspection did not allow deciding whether averages significantly differed among all or between only two groups, we performed multiple comparison testing of averages (MatLab function: multcompare.m). When parameters were compared between two groups only, we used the unpaired, two-tailed *t*-test (MatLab function: ttest2.m; The MathWorks).

Computer Simulations

To interpret experimental results, changes of 3D eye positions due to modifications of active or passive forces of extraocular muscles were simulated on computer (EyeLab,[19] a software package based on Orbit ver.1.5[20] and written in MatLab; The MathWorks). Both packages incorporate rigid pulleys in stereotypic positions.

RESULTS

Figure 1A shows the vertical deviations between the two eyes during straight-ahead viewing with the right eye covered, in healthy subjects and in patients with trochlear nerve palsy. Note that, for the purpose of analysis, eye positions in patients with left-side palsy were mirrored, so that in all patients the right eye was considered the paretic eye (see Methods section). In healthy subjects, the vertical deviation was small (average: 0.3° ± 0.5° SD), whereas in patients with trochlear nerve palsy the relative upward deviation of the paretic eye ranged widely from 0.4° to 18.2° (average: 7.8° ± 4.7° SD).

As mentioned in the introduction, discriminating between acquired and congenital trochlear nerve palsies depends on clinical impression, because validated criteria are lacking. The factor that is easiest to quantify and signifies acquired trochlear nerve palsy is a hyperdeviation of the paretic eye that increases with downgaze and when both eyes are looking toward the side of the unaffected eye. With the paretic eye covered and the unaffected eye fixing targets at 20° to the left (adduction of paretic eye, abduction of the unaffected eye), we plotted the difference between the vertical positions of the two eyes as a function of the vertical position of the viewing nonparetic eye. The gradient of vertical deviation, g_y, is obtained by determining the slope of the first-order linear regression through this scatterplot. A vertical gradient of $g_y = -0.1$, for instance, means that the hyperdeviation of the covered paretic eye increases by 0.1° with every degree of downward movement by the viewing, unaffected eye. Figure 1B shows g_y in healthy subjects and in patients with trochlear nerve palsy. In healthy subjects, the range of g_y was very small (average: 0.019 ± 0.035 SD), whereas the data in the patients scattered well above and below zero (average: −0.069 ± 0.121 SD).

For both groups of patients with trochlear nerve palsy Figure 1C depicts the vertical deviations between the two eyes during straight-ahead viewing with the paretic (right) eye covered. Averages of vertical deviations were well above the range of normal values (shaded area, average ± 2 SD) in both the acquired and the congenital groups.

Figure 1D illustrates the gradient of vertical deviation g_y in the two groups. Whereas the values measured in patients with acquired trochlear nerve palsy tended to be below zero, they were approximately zero in patients with congenital trochlear nerve palsy. The averages of the gradient g_y differed signifi-

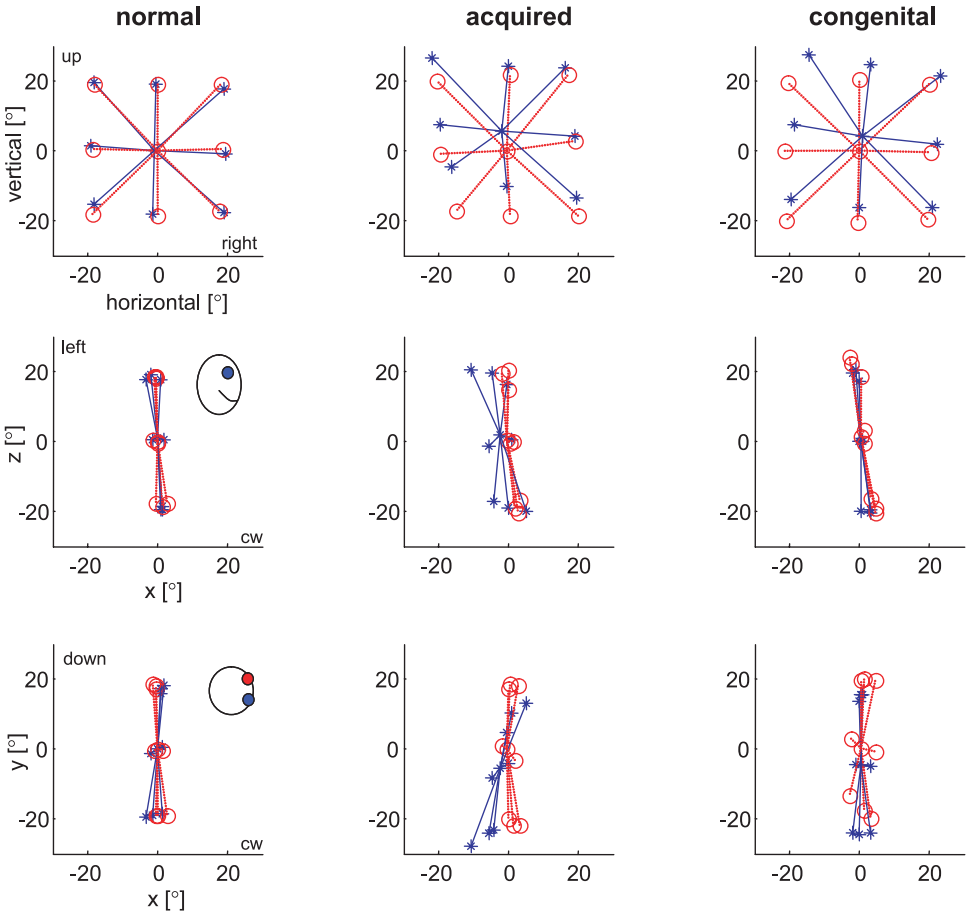

FIGURE 2. Examples of 3D eye position during the modified Hess screen test. *Red open circles* connected with *dotted lines*: left viewing eye. *Blue asterisks* connected with *solid lines*: right covered eye. *Left column*: healthy human subject (KN); *middle column*: patient with acquired trochlear nerve palsy (IM); *right column*: patient with congenital trochlear nerve palsy (SB). In the two patients, the covered right eye was the paretic eye. *Top row*: standard Hess screen plot of horizontal–vertical directions of the lines of sight of both eyes (positive: right, up). The computation of gaze direction from a rotation vector is given elsewhere.[16,24] *Middle row*: side view of rotation vectors; cw, clockwise. *Bottom row*: top view of rotation vectors. Note that in the *middle* and *bottom rows* the signs of the three eye position components (torsional, vertical, horizontal) follow the right-hand rule (positive: down, left, and clockwise as seen by the subject). *Insets*: head positions for the side and top views of the rotation vectors (*blue*, right eye; *red*: left eye).

cantly between the patients with acquired and those with congenital disease (unpaired, two-tailed *t*-test: $P < 0.01$).

Figure 2 depicts typical examples of 3D median eye positions in a healthy subject (left column), a patient with right-side acquired trochlear nerve palsy (middle column), and a patient with right-side congenital trochlear nerve palsy (right column).

In the standard Hess screen plot (Fig. 2, top row), the comparison between horizontal-vertical gaze directions of the healthy subject (normal) and of the patients (acquired, congenital) revealed the typical binocular consequences of trochlear nerve palsies. In the healthy subject (KN), the horizontal–vertical deviations between the two eyes were minimal. On the contrary, in both patients the covered paretic eye (right eye) showed an upward deviation from the viewing unaffected eye (left eye). This vertical deviation increased with left gaze. In the patient with acquired trochlear nerve palsy (IM), the vertical deviation between the two eyes also increased in downgaze, which is a classic finding in patients with acquired trochlear nerve palsy without clinical overaction of the antagonistic inferior oblique muscle.[6,7] In the patient with congenital trochlear nerve palsy (SB), however, the vertical deviation increased on up and left gaze.

Plotting 3D rotation vectors from the right side (Fig. 2, middle row) demonstrates the pitch orientation of Listing's plane. Note that in our experiments the head position in the space-fixed coil frame was defined by the earth-horizontal orientation of the bite bar (see the Methods section). Listing's plane of the right eye in the patient with acquired trochlear nerve palsy appeared "thicker" because it was rotated considerably out of the *y*– *z* plane (the frontal plane) of the coordinate system in the temporal direction.

Seen from above (Fig. 2, bottom row), the Listing's planes of the two eyes in the healthy subject were both rotated temporally by a few degrees. Thus, the planes were not exactly parallel. In the patient with acquired trochlear nerve palsy, the Listing's plane of the paretic right eye showed a large temporal rotation, whereas the plane of the unaffected eye remained close to the *y*-axis of the coordinate system. In the patient with congenital trochlear nerve palsy, the Listing's planes of both eyes were oriented similar to that in the healthy subject. To determine primary position of each eye, a plane was fitted to the 3D eye rotation vectors $\mathbf{r} = (\mathbf{x}, \mathbf{y}, \mathbf{z})$ at the nine directions of gaze

$$x = \alpha_0 + \alpha_1 \cdot y + \alpha_2 \cdot z$$

where α_0 is the torsional offset, α_1 the *y*-slope, and α_2 the *z*-slope of the plane. For every gaze direction, the duration of fixation was not exactly the same. To ensure that unequal numbers of data points would not bias the planar fit, the median eye position was computed for each gaze direction. The fitting was then applied to the population of nine median eye positions. The horizontal (p_h) and vertical (p_v) components of primary position in degrees with signs as in the standard Hess screen test (rightward and upward positive) were directly computed from the slopes of the regression[24]

$$p_h = 2 \cdot \alpha_1 \cdot \frac{180}{\pi}, \quad p_v = -2 \cdot \alpha_2 \cdot \frac{180}{\pi}$$

In the top panels of Figure 3, we plotted primary positions of both eyes (right eyes: asterisks; left eyes: open circles) in the

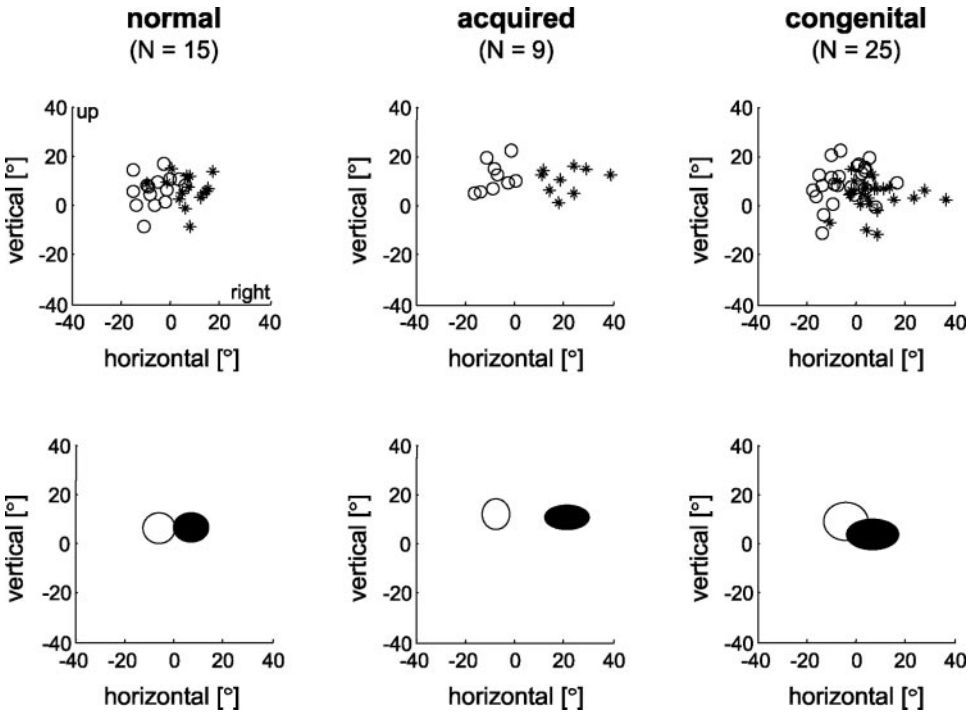

FIGURE 3. Primary positions of both eyes in healthy subjects and patients with acquired or congenital trochlear nerve palsy. Data points always refer to the viewing condition with the other eye covered. *Top row*: individual data from right (*asterisks*) and left (*open circles*) eyes. *Bottom row*: *filled ellipses*, average primary position of right eyes ±1 SD; *open ellipses*: average primary position of left eyes ±1 SD. *Left column*: healthy subjects; *middle column*: patients with acquired trochlear nerve palsy; *right column*: patients with congenital trochlear nerve palsy.

groups of healthy subjects, patients with acquired nerve palsy, and patients with congenital trochlear nerve palsy. Corresponding averages ±1 SD in the horizontal and vertical directions are shown in the bottom panels. In healthy subjects and in patients with congenital trochlear nerve palsy, the average primary positions of both eyes were located a few degrees in the temporal direction, with some overlap of the data clouds in the center. The average primary position of the paretic eye in patients with acquired trochlear nerve palsy, however, was displaced temporally by approximately 20°, whereas the average primary position of the unaffected eye was considerably closer to the vertical midline. In patients with congenital trochlear nerve palsy, the average primary position of the paretic eye was somewhat below the average primary position of the unaffected eye. No vertical divergence of primary positions was appreciable in the two other groups.

Figures 4A and 4B summarize the primary positions (average ± 1 SD) of both eyes in the three groups (circle: healthy subjects; triangle: acquired trochlear nerve palsy; square: congenital trochlear nerve palsy). In healthy subjects, the average primary positions of both eyes were symmetric. The left eyes, which were the unaffected eyes in the patients, all showed similar temporal locations of primary positions. Likewise, the average vertical locations of primary position of the left eyes were similar at approximately 10° above the horizontal meridian. The right eyes, which were the paretic eyes in the patients, showed greater differences in temporal location of the primary position among groups (one-way ANOVA: $P < 0.01$). Whereas the horizontal locations of primary position in patients with congenital trochlear nerve palsy and healthy subjects were similar, again ranging around 5° (as in the left eyes), the average primary position of the paretic eyes in patients with acquired trochlear nerve palsy was temporally rotated by more than 20°. Furthermore, there was a significant difference between the average vertical locations of primary position among the three groups (one-way ANOVA: $P < 0.01$). The multiple

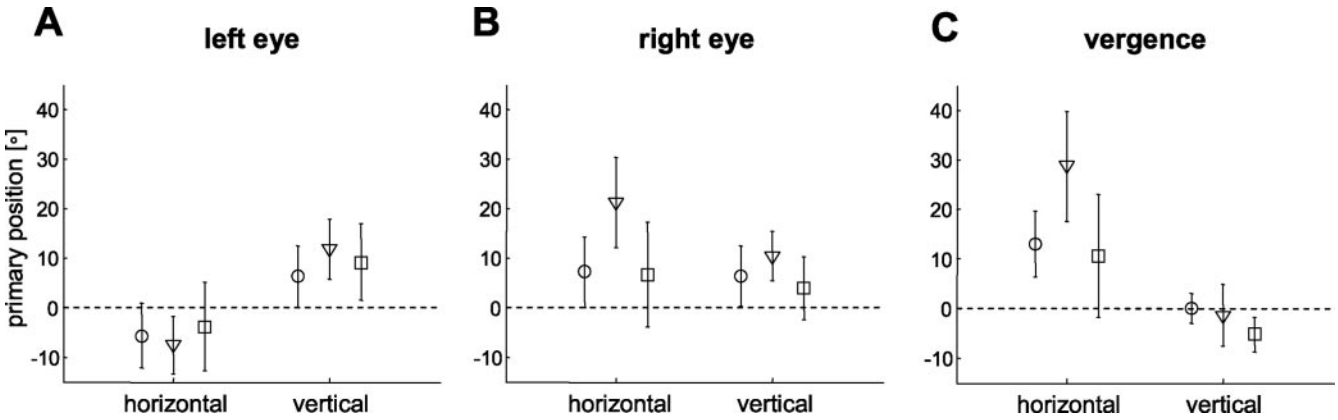

FIGURE 4. Location of primary positions of the two eyes in healthy subjects (○) and in patients with acquired (▽) or congenital (□) trochlear nerve palsy. In the patients, the right eye is always paretic and the left eye unaffected. (**A**) Average horizontal and vertical primary positions of the left eyes. Error bars denote ±1 SD. (**B**) Average horizontal and vertical primary positions of the right eyes. (**C**) Average horizontal and vertical vergence of primary positions of the two eyes. (**B**, **C**) Symbols as in (**A**).

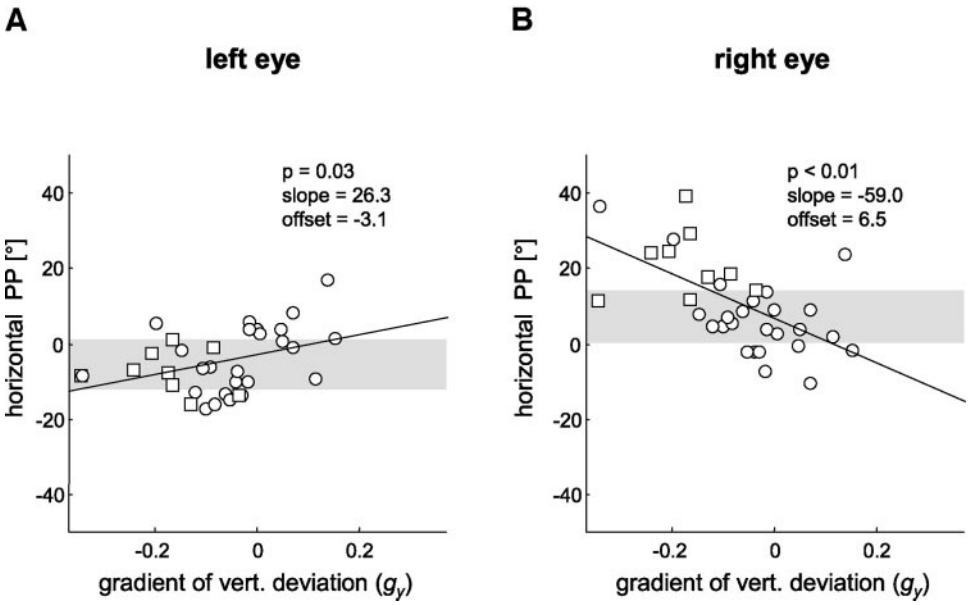

FIGURE 5. Horizontal component of primary position (PP) of the left (**A**) and right (**B**) eyes (determined in the respective viewing conditions) as a function of the gradient of vertical deviation during vertical fixations 20° to the left with the right eye covered (g_y). *Shaded area*: average horizontal component of primary position ±1 SD measured in the comparison group of healthy subjects. Patients with (□) acquired or (○) congenital trochlear nerve palsy.

comparison test of averages revealed that only the two patient groups differed significantly, with the primary position of the paretic eye being significantly lower in the patients with congenital trochlear nerve palsy.

Figure 4C displays vergence of primary positions in the group of healthy subjects and the two groups of patients. Vergence of primary positions was computed by subtracting the primary position of the left eye from the primary position of the right eye in both the horizontal and vertical directions. All three groups showed a horizontal divergence of primary positions, but the average value in patients with acquired trochlear nerve palsy was significantly different (one-way ANOVA: $P < 0.01$), and the difference was approximately three times larger than in healthy subjects or in patients with congenital trochlear nerve palsy. There was also a significant difference between the average vertical divergences of primary positions (one-way ANOVA: $P < 0.01$), but the only significant difference in the multiple comparison test of averages was between healthy subjects and patients with congenital trochlear nerve palsy. The negative vertical divergence of primary positions in the patients with congenital trochlear nerve palsy implies that the average primary position of the paretic eye was lower than the average primary position of the unaffected eye.

For each eye, the validity of Listing's law was expressed by the SD of all nine data points from the best-fit plane, the so-called thickness of Listing's plane. In neither eye was this parameter significantly different among the healthy subjects, the patients with congenital trochlear nerve palsy, and the patients with acquired trochlear nerve palsy (one-way ANOVA: $P > 0.05$).

We asked whether the horizontal and vertical divergence of primary positions in the healthy subjects and the patients were related to the amount of horizontal and vertical deviation between the two eyes during gaze straight ahead. This was tested by pooling the data of all three groups (group of healthy subjects and groups of patients with congenital or acquired trochlear nerve palsy). There was a significant ($P = 0.049$), but weak ($R = 0.28$), correlation between the horizontal divergence of primary positions and the horizontal deviation between the two eyes with the paretic eye covered (not shown). No significant correlations were found in the scatterplots: horizontal divergence of primary positions versus vertical deviation, vertical divergence of primary positions versus horizontal deviation, and vertical divergence of primary position versus vertical deviation.

We have shown that the gradient of vertical deviation between the two eyes, as a function of vertical eye position with the paretic eye in adduction (g_y), was significantly different between patients with congenital and those with acquired trochlear nerve palsy (see Fig. 1D). Also, in both groups, there was a significantly different temporal location of primary position of the paretic eye (see Fig. 4B). We asked whether there was a correlation between gradient g_y and the horizontal components of primary position in the two eyes. The scatterplots of the pooled data from the two patient groups are shown in Figure 5.

For the paretic eyes (Fig. 5B), there was high correlation between the horizontal location of primary position and the vertical gradient during leftward gaze g_y ($R = 0.59$; $P < 0.01$). Thus, the temporal displacement of primary position of the paretic eye in adduction appears to be related to an increasing vertical deficit in downgaze. For the unaffected eyes (Fig. 5A), the correlation between the horizontal location of primary position and the vertical gradient during leftward gaze (g_y) was weaker, but still significant ($R = 0.38$; $P = 0.026$). The slope of this linear regression for the unaffected eye was reversed—that is, the horizontal location of the primary position was more nasal, as the vertical deviation became larger in upgaze than in downgaze.

To test the impact of presumed alterations of eye muscle mechanics on 3D eye rotations, we performed computer simulations of innervation or length changes of the superior and inferior oblique muscles (EyeLab, the MatLab implementation[19] of the Orbit model,[20]; The MathWorks) which includes passive eye muscle pulleys. The purpose of these simulations was not to determine the exact cause of our patients' strabismus, but rather to guide our thinking about mechanisms that might explain the different patterns of kinematic changes shown by our patients. Figure 6 depicts the nine simulated standard eye positions of a healthy subject (first column), in a patient with a right-side complete superior oblique muscle palsy, without (second column) and with (third column) a simulated ipsilateral inferior oblique overaction, and in a patient with an increased length of the superior oblique and a decreased length of the inferior oblique muscles (fourth column). The palsy of the superior oblique muscle was simulated

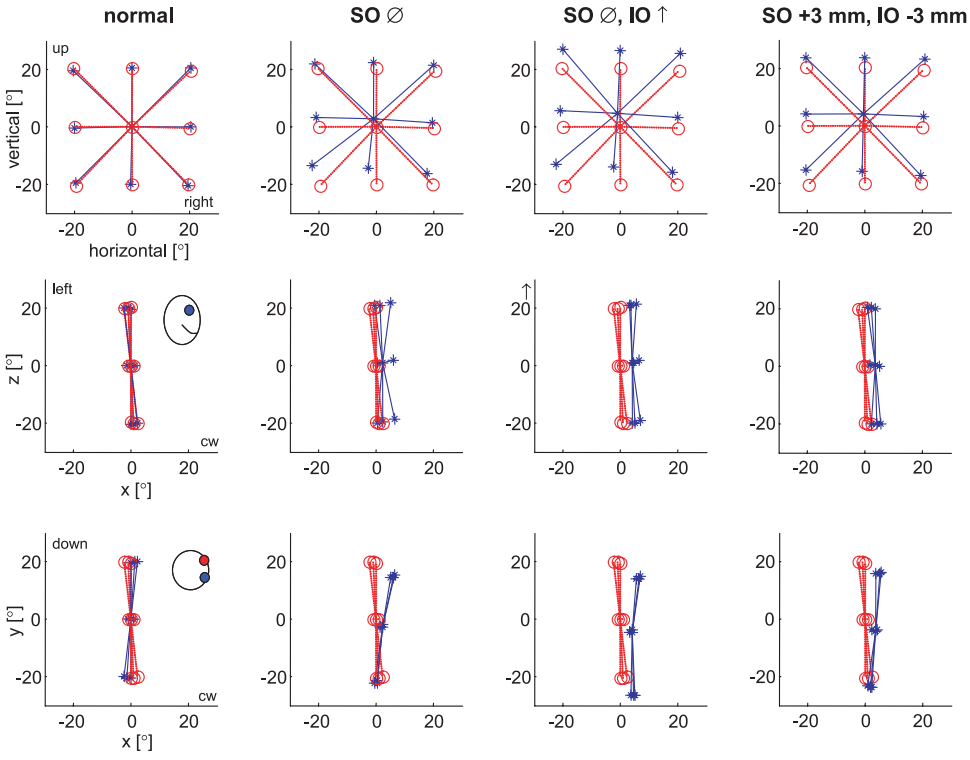

FIGURE 6. Computer simulation of binocular 3D eye position in a healthy subject (normal), a patient with right-side trochlear nerve palsy (SO Ø; total loss of active and passive forces of the superior oblique muscle), a patient with right-side trochlear nerve palsy and compensating overaction of the inferior oblique muscle (SO Ø, IO ↑; additional increase of the active force of the inferior oblique muscle by 100%), and a patient with changes in the lengths of the oblique eye muscles in the right orbit without a neural lesion (SO +3 mm, IO −3 mm; relaxed muscle lengths of the superior oblique muscle increased by 3 mm, of the inferior oblique muscle decreased by 3 mm). The orientations of the Listing's planes of both eyes in the healthy subject represent the average Listing's planes measured in the control group. These "normal" planes were the baselines for the simulations of the pathologic eye positions. Compare this figure with actual data in Figure 3. SO Ø resembles an acquired trochlear nerve palsy, SO Ø, IO ↑ and SO +3 mm, IO −3 mm a congenital trochlear nerve palsy. *Top row:* standard Hess screen plot of horizontal–vertical directions of both eyes' lines of sight; *middle row:* side view of rotation vectors; cw, clockwise. *Bottom row:* top view of rotation vectors. Note that in the *middle* and *bottom rows* the signs of the three eye position components (torsional, vertical, horizontal) follow the right-hand rule. *Insets*: symbolize head positions for the side and top views of the rotation vectors (*blue*: right eye; *red*: left eye).

by canceling both the active and passive forces of this muscle. The simulated baseline primary positions of the two eyes in the normal subject (first column) were chosen to coincide with average primary positions computed in the comparison group of healthy subjects.

Without compensatory overaction of the inferior oblique muscle (Fig. 6, second column), the covered paretic eye deviated from its fellow eye as expected in classic acquired trochlear nerve palsy: The hyperdeviation of the right eye increased with downgaze, especially in adduction (standard Hess screen plot: second column, top panel). Furthermore, Listing's plane of the paretic right eye rotated temporally. This rotation was more pronounced in downgaze than in upgaze, which, as seen best from the top view, resulted in a small curvature of the surface along the *y*-axis (second column, bottom panel) and hence a violation of Listing's law. Unfortunately, the natural thickness of Listing's plane (reflecting variability in torsional eye position) precluded us from appreciating such a small change in our patient data.

When, for compensation, the active force of the inferior oblique muscle was increased by 100% (Fig. 6, third column), the vertical deviation between the two eyes became more comitant (standard Hess screen plot: third column, top panel), a common feature in congenital trochlear nerve palsy. Listing's plane rotated back in the nasal direction, but the small curvature along the *y*-axis remained (fourth column, bottom row). In addition, there was an overall increased extorsion of the paretic eye, leading to a positive shift of Listing's plane along the *x*-axis of the coordinate system (third column, middle and bottom panels). This extorsional shift of eye positions would not appear in our search coil recordings, because actual measurements are referenced to the torsional eye position during straight-ahead viewing.

We also simulated changes in the length of the superior and inferior oblique muscles. For illustration, the relaxed muscle length of the superior oblique muscle was increased by 3 mm, and the relaxed muscles length of the inferior oblique muscle decreased by 3 mm (Fig. 6, fourth column). These changes in length also led to a hyperdeviation of the affected eye, which was less noncomitant than in the simulation of isolated acquired trochlear nerve palsy. The overall orientation of Listing's plane was similar to that in the simulation of trochlear nerve palsy with inferior oblique muscle overaction, but Listing's law was obeyed better, in that there was no curvature of the plane along the *y*-axis of the coordinate system.

Figure 7A demonstrates the effects of superior oblique palsy and compensating inferior oblique overaction on the horizontal and vertical location of primary position. Here, we discuss the results of the simulation with the paretic eye viewing. Again, the primary position of a healthy right eye was chosen to coincide with the average primary position of right eyes (7.2° right, 6.4° up) in the comparison group of healthy subjects (Fig. 7A, filled square). Setting the active force of the superior oblique muscle to zero—that is, canceling the active force of this muscle—moved the primary position 15.6° in the temporal direction and 2.2° downward (Fig. 7A, open circle). The effect of canceling both the active and passive forces of the superior oblique muscle (e.g., if the superior oblique muscle were congenitally absent) was similar; primary position moved 13.3° in the temporal direction and 3.7° downward (Fig. 7A, filled circle).

To reverse completely the horizontal displacement of primary position from normal due to superior oblique palsy (no active and passive forces along this muscle), the active force of the inferior oblique muscle had to be increased by 71% (Fig. 7A, open triangle). When, in addition, the stiffness of the inferior oblique muscle was increased by 100%, the innervation of this muscle had to increase by 161% to move primary position back to normal. This, however, resulted in an additional downward movement of primary position by 1.4°. Per-

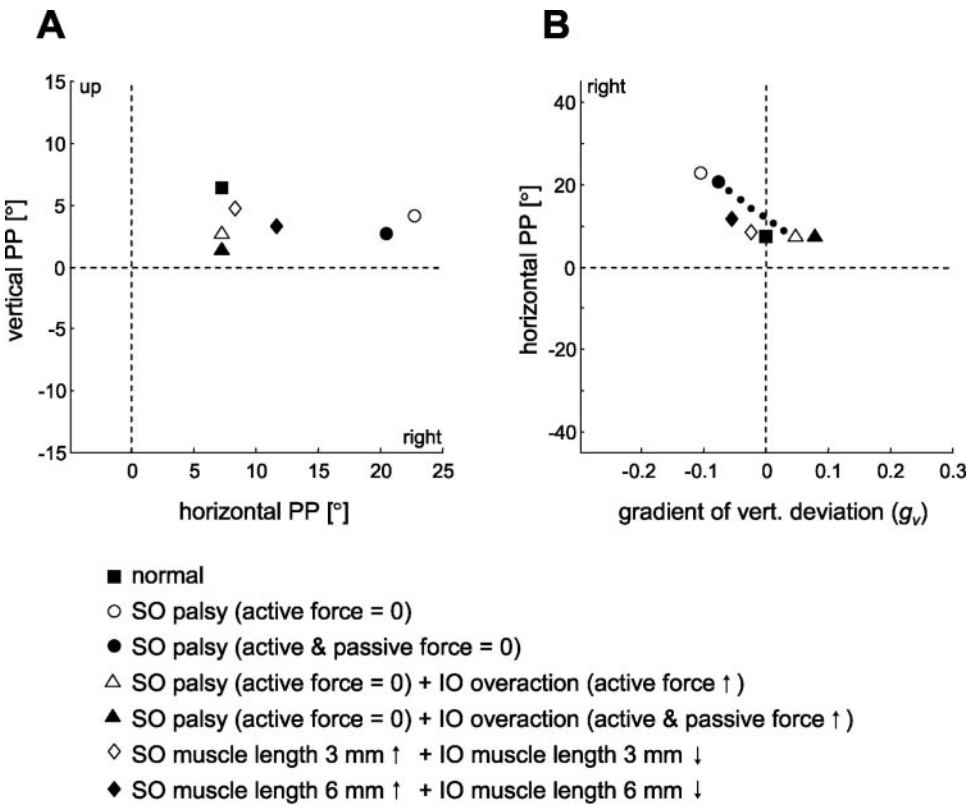

FIGURE 7. Simulation of superior oblique muscle palsy without and with overaction of the inferior oblique muscle or changes in muscle length of these two muscles. (**A**) The horizontal and vertical components of the primary position. Normal primary position of the right eye coincides with the average primary position in the group of healthy subjects. Primary position moves temporally and slightly downward when the active force of the superior oblique muscles is canceled (○) or both the active and passive forces of this muscle are set to zero (●). To reverse the temporal displacement of primary position due to superior oblique palsy (no active and passive forces), the inferior oblique muscle has to increase its active force by 71% (△). If the stiffness of the inferior oblique muscle has increased by 100%, however, the active force must reach 161% (▲). Increasing the length of the superior oblique muscle by 3 mm and decreasing the length of the inferior oblique muscle by 3 mm has little effect on the location of primary position (◇). Doubling these length changes (6 mm each) moved the primary position 4.5° temporally from its normal location (◆). (**B**) The horizontal component of the primary position as a function of the gradient of vertical deviation in adduction of the paretic eye (g_v). Symbols are as in (**A**). The active force of the inferior oblique muscle was increased in 10% steps (*small filled circles*, from left up to right down) from the baseline of an isolated superior oblique palsy.

haps a combination of two changes in the inferior oblique muscle: increased stiffness (which has been demonstrated during surgery in some patients with trochlear nerve palsy[25]), and increased innervation explains why the primary position in eyes with congenital trochlear nerve palsy is slightly but significantly lower than in eyes with acquired trochlear nerve palsy (see Fig. 4).

When the superior oblique muscle was not paretic, but lengthened by 3 mm, and the inferior oblique muscle was shortened by the same amount (as in the fourth column of Fig. 6), primary position moved temporally and downward by less than 2° (Fig. 7A, open diamond). Repeating this simulation with length changes of 6 mm moved primary position temporally by 6° from normal (Fig. 7A, filled diamond)—that is, still less than half than the movement in complete acquired trochlear nerve palsy. Thus, changes of muscle length of superior (increased length) and inferior (decreased length) oblique muscles provide an alternative explanation why primary position in eyes with congenital trochlear nerve palsy is closer to the vertical meridian than in eyes with acquired trochlear nerve palsy (see Fig. 4).

Figure 7B illustrates the simulated relation between the horizontal component of primary position and the gradient of vertical deviation in adduction of the paretic eye (g_v). Note that the primary position of the paretic eye was simulated in the viewing condition, while g_v was simulated with the paretic eye covered. Starting with an isolated superior oblique palsy with both active and passive forces set to zero (Fig. 7B, filled circle), the innervation of the inferior oblique muscle was increased in 10% steps (Fig. 7B, small filled circles) from its baseline (100%) up to 171% (Fig. 7B, open triangle). Whereas the horizontal component of the primary position decreased, the gradient g_v moved from negative to positive in an almost linear fashion. Vertical comitance was reached when the increase of active force in the inferior oblique muscle was 43%. The normal location of primary position, however, was only reached when the active muscle force of the inferior oblique increased by 71%, at which point the gradient g_v had already reversed. This behavior agrees well with the linear regression through the scatterplot between gradient g_v and the horizontal component of primary position of the paretic eye in the pooled database of patients with acquired and congenital trochlear nerve palsy (see Fig. 5). Considering that the model is only a rough approximation of the real ocular motor plant, and we do not know the actual anatomic abnormalities in our patients, the similarity of slope and offset with the experimental data is striking.

The simulation of an increased length of the superior oblique muscle by 3 mm and a decreased length of the inferior oblique muscle by the same amount yielded a data point (Fig. 7B, open diamond) close to normal (Fig. 7B, filled square). Repeating this simulation while doubling the changes in length of both muscles (6 mm each) moved the data point (Fig. 7B, filled diamond) in the direction of acquired trochlear nerve palsy.

DISCUSSION

Main Findings

This study compared 3D eye positions in healthy subjects, patients with presumed acquired trochlear nerve palsy, and patients with presumed congenital trochlear nerve palsy. The paradigm consisted of ocular fixations on a Hess screen (nine different gaze directions) with one eye viewing and the fellow eye covered. The main findings were: (1) In patients with

acquired trochlear nerve palsy, the location of the primary position of the paretic eye was significantly more temporal (by approximately 15°) than in patients with congenital trochlear nerve palsy. (2) The paretic eye in patients with congenital trochlear nerve palsy showed no significantly different horizontal location of primary position than the eyes in healthy subjects. (3) Primary position of the unaffected eye in both groups of patients was not abnormally displaced. (4) For either eye, the validity of Listing's law, expressed by the SD of 3D ocular positions from the best-fit plane (thickness of Listing's plane), was not significantly different among the three groups of subjects.

Primary Position in Acquired Trochlear Nerve Palsy

For the pooled data of all subjects, no correlation was found between the horizontal location of primary position of the paretic eye and the vertical deviation between the two eyes during straight-ahead gaze. There was, however, a good correlation between the temporal displacement of primary position and the increase of vertical deviation between the two eyes with the paretic eye in adduction and gaze moving downward. This gradient of vertical deviation is an indicator of the reduction in force of the superior oblique muscle, because this muscle has its main vertical action in adduction.[26] Thus, the temporal displacement of primary position appears to be directly related to the decreased function of the superior oblique muscle.[21,27] Considering this muscle's action—a rotation of the ocular globe around an axis that lies nearly in the horizontal plane of the eye and forms an angle of approximately 43° with the sagittal axis[1]—a superior oblique muscle palsy causes the eye to change its torsional orientation as a function of gaze depression—that is, the eye develops relative extorsion with downgaze compared with normal function. Such a torsional gradient in the vertical direction implies a temporal location of primary position.[24] Because only patients with acquired trochlear nerve palsy showed the temporal displacement of the primary position of the paretic eye, we infer that, in this group of patients, other extraocular muscles of the same eye are not (or not fully) compensating for the torsional gradient in the vertical direction. Our patients showed no abnormal displacement of the horizontal component of primary position in the unaffected eye, in contrast to Wong et al.,[27] who reported temporal displacement of primary position in both eyes of patients with chronic acquired superior oblique palsy. This discrepancy is not easily explained. There were methodologic differences between the two studies (e.g., the pattern of target displacements and refixations that may affect Listing's plane,[28] and the overall displacement of the primary position in the paretic eyes of the patients in Wong et al.[27] was also larger than in our study.

Interestingly, a temporal displacement of primary position is also observed in a physiological situation: When healthy eyes converge, the primary positions of both eyes move outward.[29] In other words, during convergence, the eyes are relatively intorted in upward gaze and extorted in downward gaze, which results in a more temporal location of primary position. This phenomenon is probably due at least in part to the decreased activity of the superior oblique muscle. In fact, it has been demonstrated in alert monkeys that the firing rate of neurons in the trochlear nucleus decreases with convergence.[30] Thus, independent of whether a superior oblique muscle deficit is pathologic (palsy) or physiological (decreased activity), the eye's primary position moves in the temporal direction. Note, however, that during very close viewing, weakening of the superior oblique muscle alone may not account for the total temporal displacement of the primary position. Decreased innervation of the inferior oblique muscle or increased innervation of the superior rectus muscle may also be necessary.[31] It is also possible that translation of ocular pulleys with convergence accounts for some of this change.[32]

Primary Position in Congenital Trochlear Nerve Palsy

In contrast to patients with acquired trochlear nerve palsy, the average primary position of the affected eye showed no abnormal temporal displacement in patients with congenital trochlear palsy. Furthermore, in these patients, the average vertical deviation between the two eyes with the paretic eye in adduction did not significantly increase with downgaze. Provided that the superior oblique muscle in these patients is not exerting its normal force, we must postulate compensatory force changes in the other extraocular muscles. Of the six extraocular muscles, only the inferior oblique muscle is able to accomplish these two compensating tasks: decrease the gradient of vertical deviation in adduction, and cancel the temporal displacement of primary position. Although the lack of an increase in vertical deviation in the field of action of the paretic superior oblique muscle is commonly assigned to an overaction of the antagonistic inferior oblique muscle,[33] the influence of this muscle on the orientation of Listing's plane, and therefore on the primary position, has not been appreciated so far. Because the action of the inferior oblique muscle is extorsional-upward with an axis that nearly lies in the horizontal plane of the eye and forms an angle of approximately 39° with the sagittal axis,[1] an overaction of this muscle may cancel the relative intorsional gradient in the upward direction after superior oblique muscle palsy. In other words, an inferior oblique muscle overaction is able to decrease both the vertical and torsional noncomitance between the two eyes along vertical positions. Perhaps this relative increase in comitance allows for better binocular visual function.

Alternatively, congenital trochlear nerve palsy may not be a palsy at all, but could be the consequence of an increased length of the superior oblique muscle, with or without a decreased length of the inferior oblique muscle.[3,34] In this case too, one would expect that vertical and torsional deviations of both eyes are relatively comitant; hence, the gradient of vertical deviation with the "paretic" eye in adduction would be close to zero and the location of primary position within the normal range.

Besides abnormal length of muscles, other anatomic aberrations within the orbit could be responsible for the clinical picture of congenital trochlear nerve palsy, among them abnormal positions of ocular pulleys,[12,35] tendon anomalies,[3] or absence of muscles.[4]

Computer Simulations

The results of the computer simulations demonstrated that the orientation of Listing's plane and hence the location of primary position in patients with trochlear nerve palsy can be explained by decreased activity of the superior oblique muscle with varying degrees of "overaction" of the inferior oblique muscle. We have provided evidence that, in patients with acquired trochlear nerve palsy, the horizontal displacement of the primary position of the paretic eye is due to the reduced force of the superior oblique muscle alone. On the contrary, the finding that the horizontal component of primary position in patients with congenital trochlear nerve palsy is in the normal range can be explained by an overaction of the inferior oblique muscle compensating for the superior oblique palsy. There is considerable evidence that adaptive changes in innervation to eye muscles can be disconjugate and monocular.[36–40] Alternatively, changes in the lengths of the superior and infe-

rior oblique eye muscles without a neural lesion can explain the normal location of primary position in patients with congenital trochlear nerve palsy. We are certainly aware of the possibility that some of the patients with the diagnosis of congenital trochlear nerve palsy may have had a tendon anomaly,[3] or even an absence of this muscle.[4] Abnormal positions of ocular pulleys, too, may produce a clinical picture that simulates a superior oblique palsy,[11,12,35] and it is, of course, possible that patients with congenital trochlear nerve palsy have a combination of abnormalities.

Our experimental data also suggest that there may be changes in the unaffected eye; adaptive inferior rectus weakness could account for the change in the primary position of the unaffected eye as a function of the gradient of the vertical deviation (Fig. 5). By decreasing the active force of the inferior rectus muscle of the unaffected eye in the computer simulation, the primary position moved nasally and the vertical deviation between the two eyes during viewing toward the side of the unaffected eye became more comitant (not shown). For instance, a decrease in the active force of the inferior rectus muscle by 20% moved the primary position 4.9° in the nasal direction and increased the gradient g_y by 0.073.

Finally, despite the close approximation of our simulations to the physiological measurements in the patients, we reemphasize the caveat that, in the absence of definitive evidence of the nature of the anatomic abnormality in our patients, our inferences about pathophysiology must still be tentative. Independent of the exact orbital mechanisms, however, there are visual consequences of the temporal displacement of the primary position. When viewing targets at infinity, divergence of the primary position of the two eyes leads to torsional noncomitance during fixation along vertical lines, which leads to eye-position–dependent cyclodisparity[18] or even torsional double vision. Because, as we have demonstrated, the divergence of primary positions is larger in acquired trochlear nerve palsy than in "congenital" trochlear nerve palsy, it is not surprising that, in our clinical experience, it is mostly patients of the former group who report having torsional double vision.

Conclusions

The measurement of 3D eye position in patients with trochlear nerve palsy revealed differences of ocular kinematics between patients with acquired and congenital trochlear nerve palsy. Although in both groups of patients Listing's law was relatively preserved, the primary positions of the affected eyes differed. We have provided explanations for these differences based on an existing mathematical model of the eye plant. Further refinements of such models based on the functional anatomy of extraocular muscle and pulley positions,[35,41] as well as the implementation of active pulleys (i.e., pulleys that change their position with changes in gaze,[42]), should lead to a closer agreement between simulations of changes in the ocular motor plant and the actual experimental findings in patients.

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